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FOREWORD

The *United States Armed Forces Medical Journal* is the medium for disseminating information of administrative and professional interest to all medical personnel of the Department of Defense. The Chairman of the Armed Forces Medical Policy Council and the Surgeons General of the several services invite all medical officers, dental officers, Medical Service Corps officers, Nurse Corps officers, and officers of the Veterinary Corps of the Armed Forces, and the medical consultants of the Army, Navy, and Air Force to submit manuscripts for publication in this *Journal*.

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Monthly Message

The first session of the Section on Military Medicine of the American Medical Association is now a matter of history, for at the Chicago meeting this infant among the sections took the first formal steps in the direction of organizational maturity. Much credit is due those medical godparents who fostered this new creation through the past 3 years of its development.

Within the confines of this neophyte section are available unlimited opportunities for the dissemination of military medical knowledge and the stimulation of a common scientific interest among civilian and military physicians alike. Where the total population is exposed to the possibility of mass destruction, a universal interest in catastrophe medical care exists and the boundaries between civilian and military medicine become less distinct.

The Section on Military Medicine deserves the support of American medicine whether in or out of uniform, for here lies a common scientific trading ground of facts essential to the welfare of the civilian population as well as the members of the Armed Forces.

Melvin A. Casberg, M. D., *Chairman,*
Armed Forces Medical Policy Council
Office of the Secretary of Defense

The Current Relation Between Military and Civilian Medicine[1]

Dan C. Ogle, *Major General, U. S. A. F. (MC)* [2]

IT is difficult to maintain an objective viewpoint relative to the relationships between military and civilian medicine. There are inherent similarities, but more significantly there are basic differences in the professional, operational, and personnel factors of the 2 fields. Military medicine is at once a military and a clinical activity, each phase of which has many facets. There is a great tendency to think of military medicine as the blind men comprehended the elephant, or perhaps more accurately, military medicine is conceived by each of us in the light of our own interests and experience or in the darkness of our own preconceptions.

I believe that it is quite appropriate that this body of consultants maintain a close liaison with the Air Force Surgeon General. The effective administration of military medicine is becoming more difficult, and your continued interest is required—an interest which I am convinced stems from a mixture of patriotism, devotion to medicine, and a sincere desire to improve the medical service of the Air Force.

The difficulty of maintaining an objective viewpoint concerning the relationships between military and civilian medicine is increasingly apparent in view of the growing dependence of military medicine on the civilian medical economy and in view of broadening civilian influence and multiple controls imposed by current policies and circumstances.

Surgeons general of military forces a short time past operated within the walled confines of a rigid military structure. Their word was law, both operationally and professionally. In military medical fields they exercised combined executive, legislative, and judicial powers. They

(1) Presented at the semiannual conference of the national consultants to the Surgeon General of the Air Force, Washington, D. C., 22-23 May 1952.

(2) Deputy Surgeon General, U. S. Air Force.

also controlled medical research, teaching, and practice procedures within their purview. They could accept or reject from the abundance of applicants for military medical careers. Procurement was no problem; the retention of a man in the service presented no problem; and men facing the possibility of retirement for physical disability frequently enlisted private counsel to help prove their right to remain in the service. The military medical man was economically secure, socially accepted, professionally recognized, occasionally envied, and rarely overworked. His promotions were automatic, and with any luck at all his honorable retirement was assured. This was not a picture of indolence, and during such periods military medical men successfully met many scientific challenges and made as important per capita contributions to the great body of medical knowledge as came from civilian sources.

Today the situation is different. The need for a stable core of military medical specialists is greater than ever before. Military tactics and weapons are infinitely more complex. There is a close integration of all forms of warfare, land, sea, and air; the distribution of forces is global; and units are so mobile that single battle complexes may run the whole gamut of geographic and climatic variations. Medical practice itself is infinitely more complex as is military medical management. This era of specialization, dispersion, and complex world politics has resulted in an interdependence of nations, forces, systems, and medical disciplines, both military and civilian. In military medical fields we are striving to organize and administer this interdependence into an equitable and effective system.

A surgeon general is no longer the unquestioned autocrat he used to be. He is still responsible for the administration and management of his departmental medical service, but, in fact, he has become a coordinator, a front man, a representative, and a perennial committeeman. He is responsible not only to his chief of staff and departmental secretary but also to other military departments and bureaus, to Congress, to organized American medicine, to friendly and co-operative nations, to innumerable committees and boards, and to each member of the military establishments, including their families and friends.

This state of integrated confusion started about 10 years ago when we found ourselves engaged in a global war. We were unprepared to plan and meet military requirements to everyone's satisfaction. People overlooked poor planning in many areas, but not in medicine, and the idea of criticism caught on so well that by the end of 1945 many people were convinced that military medical management needed overhauling and the program as it existed had to be replaced. Confidence and respect for military medicine declined, but the basic structure was maintained by a small hard core of careerists who were willing to identify themselves with a military structure and who firmly believed in the continuing need of a military medical service. The need for reconstituting military medicine was recognized. The entangled processes,

still in progress, constitute a real threat which necessitates the mobilization and conservation of our national resources, including medical resources.

I shall mention some of the various influences that have been brought to bear on the complexion of military medicine in the past 5 years. In 1947 the military departments were still under severe criticism for the manner in which military medical matters had been managed throughout World War II. Military medicine was definitely unpopular, and the military departments, recognizing weaknesses and difficulties attendant to their medical services, instituted processes designed to strengthen these services. Many studies were made at very high levels. There were numerous consultations with civilian medical experts and the military consultants of World War II organized as a specific unit to assist in managing the Army's military medical program.

In the fall of 1947 the new Secretary of Defense considered the establishment of a triservice committee on military medicine which was established officially in January of 1948. This committee met regularly over a period of 18 months, and through a system of 22 subcommittees studied the entire field of military medicine, making pertinent recommendations as to its improvement. Within the structure of the Hoover Commission, the Eberstadt Committee made an exhaustive study of the military medical situation, as did the Voorhees Subcommittee. Subsequent to the report of the Hoover Commission and up to the present time, a special physicians committee has taken an active interest in the military and Federal medical situation. Near the close of the activities of the triservice committee, the Secretary of Defense believed he needed continuing advice relative to the administration of military medical affairs and as a consequence another medical advisory committee was established under the Chairmanship of Mr. Cooper of the American Telephone and Telegraph Company. This committee finally gave way to a civilian director of medical services and a medical supervisory and policy office within the office of the Secretary of Defense. After a few months this medical directorate within the office of the Secretary of Defense was re-formed as the Armed Forces Medical Policy Council, which is still functioning within the office of the Secretary of Defense.

With the reinstitution of active Selective Service procedures, stimulated by the Korean campaign, and the necessity for expanding the Armed Forces, another civilian advisory committee, the Rusk Committee, was formed under the auspices of the National Security Resources Board. This committee still functions in a dual capacity as the national advisory committee relative to medical matters both to the Selective Service System and the President. Within this committee the Cummings Subcommittee now functions specifically in relation to the Federal Civil Defense Administration. The interest and activity of the American Medical Association, as well as other national associations within

health fields, were definitely increased and strengthened as regards the Federal medical situation, particularly as it relates to military medicine; and more recently to further clarify the picture, the Executive Office has constituted another committee, with Doctor Magnuson as Chairman, to study the general medical economy and medical efficiency within the nation.

Throughout this entire period Congress has made extensive studies of the total military situation, particularly military medicine, and a great number of bills have been introduced in both Houses of Congress having a definite bearing on the problem. The most significant of these bills passed by Congress was the doctor draft law, known as Public Law 779.

Within the Air Force about four-fifths of the physicians now on duty are civilians temporarily in uniform. There appears to be no immediate prospect of a decrease in this percentage. The percentage of men in the career structure of military medicine is dangerously low, and we as military medical men and as civilian consultants must do everything in our power to increase the numbers of those who by career choice and continued training will control the management of the military medical situation. This can be successfully done only by a process of education directed toward those controlling groups who believe that military medicine is (1) simply a matter of hospital beds; (2) a system of specialists who hold themselves ready to treat the various ills that men are heir to; and (3) but a necessary evil that is to be ignored except in time of pain. It is a big business and an intricate one.

We hope in this conference to point out some of the various features of our military medical problems. We beg your continued understanding and interest. We in the military services are now closely integrated with and dependent on every facet of organized American medicine from the medical school through final stages of specialization and on all the resources of supplies and facilities necessary to the practice of medicine at home, abroad, during peace, and during war. We never again will revert to the closed corporation of military medicine of which I spoke at the beginning. Whether we like it or not, these are normal times. We are faced with normal recurring problems and in some way we must successfully solve them.

Duodenal Ulcer in Military Personnel: Studies on Military Effectiveness of the Ulcer Patient

III. Review of 350 Cases of Recurrent Duodenal Ulcer

Eddy D. Palmer, *Lieutenant Colonel, MC, U. S. A. (1)*
Benjamin H. Sullivan, Jr., *Lieutenant Colonel, MC, U. S. A. (2)*
Eugene L. Hamilton, *(3)*

IN previous communications we have documented the fact that duodenal ulcer is a potent factor in the attenuation of the nation's fighting strength *(4)* and have discussed some of the medical and administrative problems in the management of soldiers who develop this disease *(5)*. During World War II most soldiers discovered to have duodenal ulcer were separated from the service. In an effort to determine whether this was a necessary or wise policy, and to discover if it is true that recurrence of ulcer activity is so frequent as to render these patients ineffective from the standpoint of manpower economy, we have undertaken a study of 350 patients with recurrent duodenal ulcer. All were military patients hospitalized at one or the other of two large army hospitals in the United States at some time during the period 1947-1951. They represent much less than one-sixth of the total number of patients with duodenal ulcer treated in these hospitals during this period. Each patient selected met all of the following criteria: (1) roentgenologic proof of a duodenal ulcer was present during the current

(1) Walter Reed Army Hospital, Washington, D. C.
(2) Brooke Army Hospital, Fort Sam Houston, Tex., and Medical Statistics Division, Office of the Surgeon General, U. S. Army.
(3) Medical Statistics Division, Office of the Surgeon General, U. S. Army.
(4) Hamilton, E. L.; Sullivan, B. H., Jr.; and Palmer, E. D.: Duodenal ulcer in military personnel: studies on military effectiveness of ulcer patient; incidence. U. S. Armed Forces M. J. 3: 831-838, June 1952.
(5) Palmer, E. D., and Sullivan, B. H., Jr.: Duodenal ulcer in military personnel: studies on military effectiveness of ulcer patient; the problem. U. S. Armed Forces M. J. 3: 455-459, Mar. 1952.

hospitalization and on at least one previous admission to a military hospital; (2) the patient had been returned to military duty following at least one previous hospitalization for a radiologically proved duodenal ulcer; and (3) no other major illness was present during the current admission which might have prolonged hospitalization or affected the disposition. This series does not include all patients meeting the criteria and hospitalized during the prescribed period; selection was based solely on availability and adequacy of the records.

In the discussion and tables which follow, "age" and "length of service" are calculated as of the date of admission to one of the two hospitals participating in the study; "duration of ulcer symptoms" was similarly calculated and was taken to begin with the first appearance of symptoms which could be clearly attributed to the disease, even though radiologic proof may have been lacking at that time. The "total period of hospitalization" is the sum of all periods, including the most recent one, spent as a military patient with duodenal ulcer; it includes time spent in transit from overseas hospitals, on convalescent leave, and while awaiting action by military boards and agencies, as well as that spent on the ward undergoing treatment. "Number of hospitalizations" represents the total number of times the patient entered a military hospital for duodenal ulcer, including the most recent admission, but does not include transfers from one hospital to another. "Complications" and "operations" are cumulative and refer to the entire period of military hospitalizations including the most recent one. "Retired" as used here represents disability separations of all types.

THE DATA

The 350 patients who met the criteria outlined above included 5 women. All patients were white except for 1 Filipino and 19 Negroes. Thirty-five percent of the group were officers and 65 percent enlisted personnel. Fifty-four percent of the enlisted patients were in the upper 3 grades and 49 percent of the officers held the rank of major or above at the time of the most recent hospitalization.

The age of the patients varied from 18 to 60 years (table 1). Of the 42 enlisted persons eventually retired, 26 (62 percent) were under 30 years of age, whereas only 2 (18 percent) of the 11 retired officers were in this age group. This is explained in part by the fact that the officer group was composed of a relatively greater number of older people than the enlisted group. For the purpose of analysis, it was assumed that the age distribution in this series was similar to the age distribution of the total Army and Air Force. Age specific indexes were constructed as follows: (1) age specific rates were calculated using an average of the age distributions of the total Army and Air Force for two periods, December 1948 and March 1949, which were roughly mid-

way in the study period; (2) the rate obtained for total cases was taken as a base of 1, and the rates for each age group were then applied to this base to obtain the indexes; i. e., each rate was expressed as a multiple or decimal fraction of the total rate. The requirement that the patient must have been hospitalized on two separate occasions creates a bias with respect to the underenumeration of the lower age groups, and, therefore, contrasts between the lowest and highest age groups in duodenal ulcer patients generally are not so great as the indexes might seem to indicate, although the trend is undoubtedly correct: that is, patients with recurrent duodenal ulcer were much more apt to be in the older age group.

TABLE 1. *Age, rank, and type of disposition of 350 patients with recurrent duodenal ulcer*

Age at admission	Age index* Total	Grand total	Officers			Enlisted		
			Total	Duty	Retired	Total	Duty	Retired
Total	1.00	350	121	110	11	229	187	42
Under 20	.19	15	0	0	0	15	14	1
20-24	.51	57	3	3	0	54	42	12
25-29	1.16	78	20	18	2	58	45	13
30-34	1.32	65	25	24	1	40	36	4
35-39	2.31	53	22	21	1	31	26	5
40-44	3.52	37	22	20	2	15	11	4
45-49	3.58	19	11	8	3	8	7	1
50-54	5.66	11	5	4	1	6	4	2
55 and over	14.59	15	13	12	1	2	2	0

*Age specific indexes calculated as described in text.

Length of service varied in these patients from less than 1 to more than 25 years (table 2). Sixty-eight percent (240) had less than 10 years' service, 23 percent (80) had less than 4 years' service, and 13 percent (47) had 20 or more years of military duty. Of the 53 patients eventually retired, 13 (25 percent) had less than 3 years of service, but 14 (27 percent) of those retired had served more than 20 years. Twenty-seven (64 percent) of the enlisted persons retired had less than 6 years of service while only 2 (18 percent) of the officers had served less than 6 years at the time of retirement.

TABLE 2. *Length of service, rank, and type of disposition of 350 patients with recurrent duodenal ulcer*

Length of service at admission (years)	Length of service index* Total	Grand total	Officers			Enlisted		
			Total	Duty	Retired	Total	Duty	Retired
Total	1.00	350	121	110	11	229	187	42
Under 1	.10	10	0	0	0	10	8	2
1-3	.91	70	6	5	1	64	54	10
4-6	1.01	87	25	24	1	62	47	15
7-9	1.32	73	29	27	2	44	37	7
10-14	1.94	36	19	19	0	17	16	1
15-19	3.99	27	15	14	1	12	10	2
20-24	5.89	26	11	7	4	15	11	4
25 and over	6.22	21	16	14	2	5	4	1

*Calculated as described in text.

Length of service specific indexes were calculated in the same manner as the age specific indexes. Average strength distributions in the total Army and Air Force for December 1948 and March 1949 were used, the total rate was considered as a base of 1, and the rate for each period of service was expressed as a multiple or decimal fraction of this base. The bias introduced by the criteria for case selection has been pointed out in the description of the age specific indexes. The index for those persons retired with from (1) 15 to 19 years of service was 2.94; (2) 20 to 24 years of service, 12; and (3) 25 or more years of service, 5.88. This was undoubtedly somewhat influenced by the fact that the laws governing retirement confer additional benefits on persons who have served at least 20 years, thus encouraging the patients whenever possible to remain in the service an additional year or two in order to secure these benefits.

Ulcer symptoms had been present for 3 months or less in 11 patients and for more than 15 years in 11 patients. Forty-four percent (154) had complaints attributed to ulcer for 40 or more months; this group included 53 percent (67) of those who had a complication or an operation and 53 percent (28) of those who were separated from the service for physical disability; but this represented 88 percent (9) of the entire group of officers retired and only 45 percent (19) of the enlisted persons retired (table 3).

TABLE 3. *Length of ulcer history on most recent admission to hospital in relation to disposition and to complications of 350 patients with recurrent duodenal ulcer*

Duration of symptoms (months)	Grand total	Officers			Enlisted			Total complications	Complications treated					
									Medically			Surgically		
		Total	Duty	Retired	Total	Duty	Retired		Total	Duty	Retired	Total	Duty	Retired
Total	350	121	110	11	229	187	42	127	78	65	13	49	39	10
3 or less	11	2	2	0	9	8	1	5	3	3	0	2	1	1
4-9	49	15	14	1	34	29	5	12	9	7	2	3	3	0
10-15	47	9	9	0	38	34	4	14	8	8	0	6	4	2
16-27	56	16	16	0	40	31	9	18	11	8	3	7	7	0
28-39	33	13	12	1	20	16	4	11	7	7	0	4	3	1
40-51	34	10	8	2	24	21	3	9	6	5	1	3	2	1
52-63	35	18	16	2	17	10	7	15	11	7	4	4	3	1
64-99	47	19	18	1	28	23	5	21	12	12	0	9	7	2
100-135	14	4	3	1	10	9	1	9	5	4	1	4	3	1
136 and over	24	15	12	3	9	6	3	13	6	4	2	7	6	1

There were 213 patients admitted to the hospital for duodenal ulcer on 2 separate occasions, 83 patients 3 times, 34 patients 4 times, 11 patients 5 times, and 9 patients from 6 to 12 times. As would be expected, those with the largest number of hospitalizations had the longer service and longer duration of symptoms.

The total period of hospitalization for duodenal ulcer varied from less than 1 to 26 months (table 4). Thirty-seven percent (131) were hospitalized 2 months or less. Of this group only 5 were retired. Thirty-four percent (102) of the 297 persons returned to duty were hospitalized between 4 and 7 months, as were 47 percent (25) of the 53 persons retired. These figures are somewhat influenced by the time, often months, required in administrative handling of board proceedings and securing approval of them. During the period covered by this study these persons were classified as hospital patients, and this time was included in the total period of hospitalization. Sixty-four percent (27) of the enlisted persons but only 18 percent (2) of the officers had less than 6 years' service at the time of their retirement for duodenal ulcer. Sixteen percent (48) of the 297 patients returned to duty spent 10 or more percent of their service time as hospital patients, and 63 percent (186) spent less than 6 percent of their service time in this status. More than half (28) of the 53 persons retired spent 10 or more percent of their period of service as hospital patients, but 6 of these were hospitalized during 20 or more percent of their time in the service. Even among those retired for duodenal ulcer, 47 or about 90 percent were present for duty four-fifths of the time.

TABLE 4. *Total period of hospitalization of 350 patients with recurrent duodenal ulcer*

Months in hospital	Grand total	Officers			Enlisted		
		Total	Duty	Retired	Total	Duty	Retired
Total	350	121	110	11	229	187	42
Less than 1	9	1	1	0	8	8	0
1	64	18	18	0	46	45	1
2	58	17	17	0	41	37	4
3	34	13	13	0	21	15	6
4	51	21	19	2	30	25	5
5	34	11	10	1	23	20	3
6-7	42	11	10	1	31	18	13
8-9	18	9	9	0	9	8	1
10-11	15	8	7	1	7	1	6
12 or more	25	12	6	6	13	10	3

TABLE 5. *Ratio of hospital stay to duration of symptoms in 350 patients with recurrent duodenal ulcer*

Ratio of time in hospital to duration of ulcer symptoms (percent)	Grand total	Officers			Enlisted		
		Total	Duty	Retired	Total	Duty	Retired
Total	350	121	110	11	229	187	42
1 or less	8	1	1	0	7	7	0
2-2.9	17	7	6	1	10	10	0
3-3.9	18	9	8	1	9	8	1
4-4.9	20	5	5	0	15	12	3
5-5.9	11	4	4	0	7	5	2
6-7.9	47	16	15	1	31	26	5
8-9.9	29	12	12	0	17	15	2
10-14.9	43	20	19	1	23	18	5
15-19.9	38	9	8	1	29	24	5
20-24.9	21	7	5	2	14	9	5
25-49.9	58	20	18	2	38	33	5
50 or more	40	11	9	2	29	20	9

A better measure of noneffectiveness is the relation of time in the hospital to the duration of ulcer symptoms, inasmuch as this denominator indicates the relative length of time served during which personnel would actually be subject to possible hospital admission for duodenal ulcer. More than half (200) of the 350 patients spent 10 or more percent of the time during which they had ulcer symptoms in the hospital; one-third (119) were hospitalized 20 or more percent of the time, and about 10 percent (40) were noneffective for more than half of the time during which they experienced ulcer symptoms. Forty-three percent (150) of the 350 patients were present for duty 9 out of every 10 days during the period following their initial ulcer symptoms (table 5). The 350 patients studied had spent an aggregate of 3,258 years in the military service at the time of their most recent hospitalization for recurrent duodenal ulcer. There was a total of 936 hospitalizations for the group, and 139.6 patient-years were spent in hospital. Following the initial appearance of symptoms of ulcer, the members of the group served an aggregate of 1,397 years on active duty. The total period in the hospital is thus almost exactly 10 percent of the period in service after the appearance of symptoms of duodenal ulcer.

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One-third of the patients with repeated hospitalizations for duodenal ulcer had 1 of the 4 common complications of duodenal ulcer: hemorrhage, perforation, obstruction, or intractability (table 6). Hematemesis and melena were grouped together, and no criteria were established as to the extent of bleeding required for inclusion in this group, the statement of the patient or of his physician being accepted at face value. About one-fifth of the patients with hemorrhage were operated on at sometime in the course of their disease but not necessarily for the control of bleeding. A complication was present in 104 (35 percent) of the 297 patients returned to duty and in 23 (43 percent) of the 53 patients retired. Only 15, or one-third, of the cases in enlisted men retired were complicated, while 8 of the 11 cases in officers retired were so classified.

The group of patients who spent 6 or more percent of their military service in the hospital numbered 148 patients and constituted 42 percent of the entire series. It included 44 percent (56) of the 127 complicated cases and 41 percent (92) of the 223 uncomplicated cases. Seventy percent (37) of the 53 persons retired fell within this group. Sixty-five percent (15) of those retired with complications of duodenal ulcer, and 73 percent (22) of those retired with uncomplicated duodenal ulcer (table 7). We believe that the presence or absence of a complication did not significantly influence the disposition or the time spent in the hospital, but, as has been pointed out, a high proportion of the retirements were in those patients with long hospitalizations.

DISCUSSION

The disposition of a military patient with duodenal ulcer at the conclusion of his hospitalization is influenced by the patient, the physician, and the disease. The patient's motivation to remain in the service or to return to civil life will largely govern the number and severity of his subjective complaints once the ulcer is healed and will determine the frequency with which he presents himself at sick call. Many medical officers believe that "the man with duodenal ulcer who knows his diagnosis and lacks any desire to return to duty cannot be kept at duty." *(6)* They emphasize the harm done by slavish acceptance of borderline radiographic diagnoses and insist that the diagnosis of ulcer should be avoided unless the evidence is absolute because "a suggested diagnosis in the poorly motivated soldier might just as well be actual." *(6)*

The physician's attitude toward duodenal ulcer as a disease and his evaluation of the reactions of the patient are the most decisive factors in determining the disposition to be effected. Official policy will influence these decisions to a large degree and may on occasion require that all patients with duodenal ulcer be evacuated from an overseas theater or be retired from the service. The Surgeon General

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(6) Kelley, R. W.: Personal communication.

TABLE 6. *Complications in 350 patients with recurrent duodenal ulcer*

Complication	Number of patients	Percent of whole group	Percent of complications	Complication as first symptom (number of patients)	Treatment		Disposition	
					Medical	Surgical	Duty	Retired
Hemorrhage	79	22.6	62.2	28	64	15	63	16
Obstruction	11	3.1	8.7	0	6	5	10	1
Intractability	15	4.3	11.8	0	0	15	14	1
Perforation	22	6.3	17.3	13	8	14	17	5
Total	127	36.3	100.0	41	78	49	104	23

TABLE 7. *Relation of complications to disposition in 350 patients with recurrent duodenal ulcer*

History of complication	Grand total	Officers			Enlisted		
		Total	Duty	Retired	Total	Duty	Retired
Total	350	121	110	11	229	187	42
With complication	127	43	35	8	84	69	15
Treated medically	(78)	(30)	(25)	(5)	(48)	(40)	(8)
Treated surgically	(49)	(13)	(10)	(3)	(36)	(29)	(7)
No complication	223	78	75	3	145	118	27

has always provided for a certain freedom for the exercise of professional judgment by individual medical officers in even the most stringent regulations. At present great latitude exists in the interpretation of the policies governing retirement for duodenal ulcer.

In an effort to come as close as possible to an assay of the effects of the disease process itself on the loss of time from duty, this series of patients with radiologically proved recurrent duodenal ulcers was studied. From the fact that the ulcers were recurrent it may be assumed that they represented the disease in a more severe form than that of the larger group of patients with duodenal ulcer without evidence of recurrence. The incidence of complications in the series (36 percent) supports this assumption. Many of the elements tabulated reflect factors other than the effect of the disease itself. The total period of hospitalization was often prolonged by transfer of the patient from overseas hospitals, by convalescent leave, or by delay inherent in the multiple boards and agencies whose approval was required before retirement could be effected. The duration of ulcer symptoms was influenced in part by the pain threshold of the patient and perhaps in some cases exaggerated by those seeking release from service or minimized by those eager to return to duty. The number of retirements in the group with from 20 to 24 years of service was relatively greater than in the group just above and just below it, probably because of the substantially greater retirement benefits granted a man with 20 years of service but withheld from the one with 19 years. Reluctance to retire officers with duodenal ulcer is shown in each table contrasting retirements in officers and enlisted personnel. Until the current retirement law became effective, an officer was wholly retired at 75 percent of his base pay; and the decision, once approved, was irrevocable. An enlisted man's pension was dependent on the extent of his disability. This was subject to periodic review and adjustment for the remainder of his life. The attitude of physicians at present may be somewhat colored by these earlier influences. Retirement after a short period of service was often effected in an effort to minimize the financial responsibility of the Government to the soldier who developed an ulcer prior to induction, or early in his military career, and who was considered a poor risk.

In a sense, the incidence of complications is the only reflection of the severity of the disease process not subject to distortion by other factors. If the stress of military service and subsisting on field rations were important factors in the initiation of or the recurrence of duodenal ulcer, we should find most cases of ulcer and most of the complications in persons with little service. This was not true. Indeed, the incidence of recurrent ulcer was somewhat greater in those patients who were older, or had been in the service longer, probably because they had greater opportunity to acquire the disease and experience the recurrence necessary to qualify for inclusion in this series. Long hospitalization in relation to total military service was not associated with a higher

incidence of complications. The difference in the percent of those with complicated duodenal ulcer who were retired (27) and that of those with uncomplicated duodenal ulcers who were retired (24) was not significant.

The average loss of time from military duty in this group of patients with recurrent duodenal ulcer was 10 percent of the time in military service after the appearance of the initial symptoms of the disease. Although individual patients varied markedly in the amount of time lost, no method was determined for distinguishing the poor from the good risks on medical grounds alone. It is not known how to determine when it becomes uneconomical to retain a man in the military service. The cost of hospitalization and pay during this noneffective period must be balanced against the loss of money and time spent in training a man and of training a replacement should the patient be discharged. In any event, it has been shown that a large group of men with recurrent duodenal ulcer have served in the Armed Forces for a prolonged period of time. The period of noneffectiveness is significant, and perhaps uneconomical, but is not prohibitive.

SUMMARY

A study was made of 350 military patients (1) in whom roentgenologic proof of a duodenal ulcer was present during the current hospitalization and on at least one previous admission to a military hospital, (2) who had been returned to military duty following at least one previous hospitalization for a radiologically proved duodenal ulcer, and (3) in whom no other major illness was present during the current admission which might have prolonged hospitalization or affected the disposition. The rank, age, length of service, length of ulcer history, presence of complications, or surgical treatment did not significantly influence the total period of hospitalization. Complications occurred in 36 percent of the patients and did not significantly influence the total period of hospitalization or the disposition.

The 350 patients studied had spent an aggregate of 3,258 years in the military service at the time of their most recent hospitalization for recurrent duodenal ulcer. There was a total of 936 hospitalizations for the group and 139.6 patient-years were spent in the hospital. Following the initial appearance of symptoms of ulcer, the members of the group served an aggregate of 1,397 years on active duty. The total period in the hospital is thus 10 percent of the period in service after the appearance of symptoms of duodenal ulcer. Patients with duodenal ulcer can be returned to duty with the expectation that they will be noneffective for a significant but not prohibitive portion of their subsequent period of service.

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Vagotomy in the Treatment of Peptic Ulcer

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BILATERAL partial resection of the vagus nerves, or vagotomy, in the treatment of peptic ulcer has been performed on thousands of patients by a multitude of surgeons in the past 9 years, yet its place in ulcer therapy is still controversial. We are, therefore, reporting our experience with the procedure at the Fitzsimons Army Hospital in the hope that it will contribute to final evaluation of its usefulness.

GENERAL INFORMATION

Between December 1945 and December 1950, 48 vagotomies were performed in the treatment of peptic ulcer. Forty-five of the patients were considered to be suitable for analysis. Preoperative and postoperative studies included fasting gastric, histamine gastric, and insulin gastric analyses; measurements of 12-hour night secretion volumes; gastrointestinal radiography; and cholecystography. All studies except the last were repeated during the follow-up. Management before and after operation was standardized and conformed to the essentials stressed by Dragstedt (3). Patients not available for follow-up studies were sent comprehensive questionnaires at 6-month intervals. Information was also obtained by correspondence with Veterans Administration facilities and private physicians. Twenty-two patients were followed by questionnaire only; 21 by a combination of questionnaire and hospitalization; and 2 by hospitalization alone. Evaluation by questionnaire only is admittedly unsatisfactory.

Thirty-eight patients had duodenal ulcer with vagotomy (group I); 2 had gastric ulcer with vagotomy (group II); 1 had marginal ulcer with vagotomy (group III); 1 had duodenal, marginal, and jejunal ulcers with

(1) U. S. Air Force Hospital, Wright-Patterson Air Force Base, Ohio.

(2) Fitzsimons Army Hospital, Denver, Colo.

(3) Dragstedt, L. R.: Gastric vagotomy in treatment of peptic ulcers. In Cole, W. H. (editor): Operative Technic in General Surgery. Appleton-Century-Crofts, Inc., New York, N. Y., 1949. pp. 417-425.

vagotomy (group IV); 1 had duodenal ulcer with vagotomy and gastric resection (group V); 1 had duodenal ulcer with vagotomy and gastroenterostomy (group VI); and 1 had gastric ulcer with vagotomy and local ulcer resection (group VII). The length of follow-up in this series varied from 6 to 60 months. Patients requiring further treatment or experiencing ulcer recurrence are carried as dropped from the follow-up at that time.

CASE CHARACTERISTICS

In the series of 45 patients, 44 were white and 1 was a Negro. There were 44 men and 1 woman. The ages ranged from 18 to 67 years (mean 39). The chief presenting complaint was epigastric pain or discomfort; alone in 17, combined with nausea and vomiting in 27, and with additional anorexia and tarry stools in 1. The duration of symptoms ranged from 3 months to 33 years (average 11 years) prior to vagotomy.

Complications of the ulcer had occurred in 70 percent of the patients; perforation in 43 percent of these, from 1 to 8 episodes of hemorrhage in 43 percent, and both hemorrhage and perforation in 16 percent.

All patients had failed to respond to medical management and previous surgical treatment had been applied as follows: simple closure of perforation in 14; closure of perforation with gastroenterostomy, in 2; gastroenterostomy in 1; local ulcer resection in 1; and subdiaphragmatic vagotomy in 1. The average preoperative fasting total acidity was 68 units (range 4 to 144) with an average of 45 units of free HCl (range 0 to 52).

Thornton et al. *(4)* stated that in a series of normal controls the volume of night secretion for a 12-hour period ranged from 261 to 385 cc. and that the average among people with peptic ulcer was found to be 820 cc. In this series the average was 1,060 cc. (range 50 to 2,800 cc.). Preoperative roentgenographic evidence of ulcer was present in 41 patients. Of these, 6 showed obstruction, varying from minimal to 50 percent retention in 6 hours. The transthoracic approach was used in 41 patients, transabdominal in 3, and both in 1. The transabdominal route was used either because of a singificant degree of obstruction or for gastric ulcer. In no patient was there evidence of untoward effect of manipulation of the vagus nerve during operation. Postoperative complications were noted in 15 patients and consisted chiefly of pneumonitis and atelectasis. One patient developed severe distention and retention necessitating a gastric drainage and 1 developed severe hiccup which persisted for 10 days. All complications resolved without sequelas and there were no deaths attributable to operation.

(4) Thornton, T. F., Jr.; Storer, E. H.; and Dragstedt, L. R.: Supradiaphragmatic section of vagus nerves and gastric secretion in patients with peptic ulcer. Proc. Soc. Exper. Biol. & Med. 59: 140-141, June 1945.

IMMEDIATE RESULTS

The findings in this series during the first postoperative month did not vary greatly from those reported by other authors. In general, there was subjective relief from symptoms, a lowering of gastric acidity, a decrease in the volume of night secretion, and evidence of ulcer healing. Gastric atony and retention was present in many of the patients in variable degree. A summary of immediate results is shown in table 1. The 1 patient who obtained no subjective relief had a return of pain on resuming a normal diet and was discharged on a convalescent ulcer diet without symptoms. Gastric retention varied from 10 percent or less to 90 percent in 6 hours in 19 patients. The distribution was: 10 percent or less in 4; 10 to 25 percent in 6; 50 percent in 4; 75 percent in 2; and over 75 percent in 3. In a patient of the last group, obstruction and retention were severe and persistent enough to necessitate a gastroenterostomy 4 days after vagotomy. This patient was transferred from case group I to case group VI for later analysis.

Study of the immediate results revealed a parallelism between insulin test, postoperative acidity, night secretion volume, and motility. This is to be expected, but it is interesting to note that true correlation does not always exist. In this series, of the patients with a negative insulin test, there was 1 with an increase in gastric acidity with histamine; 7 revealed an increase in the volume of night secretion; and 15 revealed an increase in motility. Such unpredictable findings have been reported by others, including Walters et al. *(5)* and Moore *(6)*.

LATE RESULTS

In the evaluation of late results, a number of factors such as (1) symptom recurrence, (2) presence and severity of side effects, (3) necessity for subsequent treatment, (4) effect on body weight, working capacity, and general condition, (5) the attitude of the patient as to amount of benefit derived, and (6) the objective laboratory and roentgenographic findings must be considered. The subjective result will depend almost entirely on the recurrence of ulcer symptoms and the severity of the side effects. A recurrence of ulcer symptoms similar to those present preoperatively was experienced by 12 patients, 10 of whom were in group I, and 1 each in groups IV and VII.

The most common complaints and side effects other than symptom recurrence were: (1) foul eructations in 31 (persistent in 10), (2) distention in 29 (persistent in 9), (3) diarrhea in 27 (persistent and troublesome in 11), (4) persistent intolerance for food in 17, (5) persistent hypoglycemic episode in 16 (severe in 1), (6) persistent incisional

(5) Walters, W.; Neibling, H. A.; Bradley, W. F.; Small, J. T.; and Wilson, J. W.: Gastric neurectomy; anatomic and physiologic studies with favorable and unfavorable results in treatment of peptic ulcer. Arch. Surg. 55: 151-163, Aug. 1947.

(6) Moore, F. D.: Vagus resection for ulcer; interim evaluation; clinical results. Ann. Surg. 126: 664-678, Nov. 1947.

TABLE 1. *Immediate results of vagotomy in percent*

Group	Symptoms relieved		Insulin test					Acidity			Volume of night secretion			Roentgenographic findings		
	Yes	No	-	+	E	A	I	+	-	±	+	-	±	Healing	Atonia	Retention
I	97.3	2.7	68.4	5.2	3.6	3.6	3.6	5.3	73.7	13.1	15.8	63.2	5.2	100	63.1	50
II	100	-	100	-	-	-	-	-	-	100	50	50	-	100	+	0
III	100	-	100	-	-	-	-	-	100	-	?	?	?	100	0	0
IV	100	-	100	-	-	-	-	-	100	-	-	100	-	100	0	+
V	100	-	-	-	-	100	-	-	100	-	-	100	-	100	0	0
VI	100	-	100	-	-	-	-	-	100	-	-	100	-	100	++	++
VII	100	-	100	-	-	-	-	-	100	-	-	100	-	100	+	+

- = Negative or decrease
+ = Positive or increase
++ = Marked
± = No change
E = Equivocal
A = Achlorhydric
I = Inadequate

pain in 11, and (7) anorexia in 13 (persistent in 2). The so-called hypoglycemic episodes consisted of attacks of weakness, dizziness, and sweating, occurring in the midmorning and midafternoon. No evidence to prove actual hypoglycemia has been offered and we had no opportunity to study a patient during an episode. Three patients, however, stated that the sensation was the same as experienced during insulin gastric analyses.

Further treatment has been necessary in 18 patients, medical in 10 and surgical (gastric resection) in 8. Weight has remained below normal in 21 patients. Inability to continue the previous workload was reported by 16 patients. The general physical condition has been evaluated by 13 patients as being definitely worse since vagotomy. Satisfaction with the procedure was expressed by 25 and an additional 9 believed that the operation had helped.

Consideration of the various factors has allowed an evaluation of the subjective results which were graded as follows: (1) excellent if the patient was completely asymptomatic, (2) good if he had no ulcer symptoms, but mild symptoms from side effects, (3) fair if he had a return of ulcer symptoms, but less than preoperatively and/or moderately troublesome side effects, and (4) poor if he had a return of ulcer symptoms, ulcer complications and/or severe side effects. Using these criteria it was found that 11 had excellent results, 15 good, 3 fair, and 16 poor. The distribution as to case group is shown in table 2.

TABLE 2. *Subjective results*

Result	Case group							Total
	I	II	III	IV	V	VI	VII	
Excellent	9	2						11
Good	13				1	1		15
Fair	2					1		3
Poor	13		1	1			1	16

When comparing the follow-up objective results, as derived from study of gastric motility, retention, secretion volume, and acidity, with subjective results we found 9 patients in whom correlation was not possible. Five reported relative freedom from symptoms, but studies in all revealed atony, retention of 25 percent or more in 6 hours, and a return of gastric acidity to preoperative levels or higher. In 1 of the 5 there was marked deformity of the body of the stomach, the cause of which was unknown. There was no supporting roentgenographic or laboratory evidence to account for the ulcer symptoms or severe side effects complained of by 4. The important factors concerned in the 16 failures are recorded in detail in table 3.

TABLE 3. *Factors concerned in failures*

	Patient															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Age (years)	50	24	26	18	25	36	30	40	23	34	31	41	43	32	42	58
Group	I	I	I	I	I	I	I	I	I	I	I	I	I	III	IV	VII
Duration of symptoms	23 yr.	3 yr.	14 mo.	6 mo.	3 mo.	6 mo.	5 yr.	2 yr.	3 yr.	3 yr.	7 yr.	3 yr.	4 yr.	6 mo.	20 yr.	1 yr.
Length of follow-up (mo.)	12	60	26	6	27	24	30	12	56	36	25	33	60	36	6	50
Preoperative perforation	0	0	0	1	1	1	1	1	1	1	0	2	1	0	1	0
Preoperative hemorrhage	8	0	1	0	0	0	2	0	?	2	0	0	0	2	3	0
Acidity																
Preoperative	?	?	T-33 F- 0	T-79 F-62	T-88 F-75	T-96 F-72	?	T-92 F-66	T-72 F-30	T-77 F-65	T-67 F-50	T-81 F-75	T-107 T- 81	T-60 F-40	T-61 F-46	T-144 F- 52
Postoperative	?	?	T-15 F- 5	T-56 F-13	T-20 F- 0	T-63 F-30	T-40 F-32	?	T-24 F- 8	T-42 F-12	T-38 F-27	T-39 F-15	T-12 F- 6	T-30 F- 2	T-24 F-14	T-60 F-20
Follow-up	?	?	?	?	T-86 F-50	T-68 F-52	?	?	T-84 F-78	T-52 F-36	T-50 F-42	T-38 F-10	?	T-30 F-18	?	T-30 F-10
Insulin test																
Postoperative	?	?	I	E	-	+	-	?	-	-	-	-	-	-	-	-
Follow-up	?	?	?	?	-	+	?	?	+	+	+	-	+	-	?	-

TABLE 3. *Factors concerned in failures*—Continued

	Patient															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Volume of night secretion (cc.)																
Preoperative	?	?	1,320	620	600	?	1,000	?	800	800	750	2,000	900	0	1,050	800
Postoperative	?	?	3,000	600	600	500	1,600	?	250	?	240	650	4,000	?	450	300
Follow-up	?	?	?	?	750	?	2,000	?	700	420	525	300	?	?	?	?
Troublesome side effects	+++	+++	++	+	+++	+++	+++	++	++	++	+	+++	++	+++	0	+++
Retention (percent)	?	25	50	0	25	70	50	80	25	10	60	90	70	0	0	75
Atony	?	++	++	?	+++	+++	+++	+++	+	++	+++	+++	+++	++	?	+++
Time between vagotomy and recurrence of symptoms (mo.)	10	6	6	6	-	18	-	10	18	30	15	-	32	-	6	8
Subsequent treatment	S	M	M	M	S	M	S	M	M	S	S	S	S	M	M	S

TABLE 3. *Factors concerned in failures*—Continued

	Patient															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Remarks	Death due to volvulus after gastric resection 12 months after vagotomy.	Symptoms partially controlled by diet, banthine, and mucotin.	Symptoms partially controlled. Lost to follow-up.	Lost to follow-up.	Gastric resection to relieve retention with vomiting and anorexia 27 months after vagotomy.	Lost to follow-up 24 months after vagotomy.	Gastric resection for relief of vomiting and foul belching 24 months after vagotomy.	Lost to follow-up.	Active ulcer demonstrated 50 months after vagotomy.	Gastric resection 34 months after vagotomy.	Gastric resection for gastric ulcer 25 months after vagotomy.	Gastric resection for relief of retention and side effects 12 months after vagotomy.	Gastric resection 59 months after vagotomy.	Patient had severe hemorrhages. No ulcer seen by x-ray examination.	Lost to follow-up.	Gastric resection for large recurrent gastric ulcer.

T = units of total acidity.
F = units of free acidity.

\+ = Positive or increase
− = Negative or decrease
++ = Marked

+++ = Severe
S = Surgical
M = Medical

ANALYSIS OF RESULTS

In this series of 45 patients, 16 (35.5 percent) were classified as failures. Of these 13 (39.4 percent) occurred in the 38 patients with duodenal ulcer treated by vagotomy alone. In the patient with a marginal ulcer following gastroenterostomy, vagotomy was considered a failure because of repeated severe hemorrhages although no other symptoms were present. Another failure occurred in the patient with a duodenal, marginal, and jejunal ulcer. The remaining failure was in the gastric ulcer patient who underwent excision of the ulcer and vagotomy. Although no conclusions may be drawn from the 3 single failures, it is believed that useful information may be obtained from the 38 patients with duodenal ulcer who were treated by vagotomy alone.

The statement that the procedure is useful in the younger patients whose stomachs have good tone has appeared in the literature. Our experience does not confirm such a statement. Another question which arises is, does the duration of symptoms prior to vagotomy influence the final result? No significant correlation existed in this series. Failures were evenly distributed throughout the full range of 6 months to 30 years.

Do previous complications such as perforation and hemorrhage play a role in the result? This series appears to indicate that they do. Of 19 patients with a history of previous perforation, 10 experienced a poor result from vagotomy. The percent of failures (52.6) is thought to be significantly greater than the general percent of failures (39.4). Previous hemorrhage did not play as important a role. Of the 19 patients who had had hemorrhage, the results were classed as failures in only 5 and 3 of these had both hemorrhage and perforation. The conclusion must not be drawn that ulcer activity or intrinsic inability to limit the progress of the disease is the only factor at play in this phenomenon. The presence of varying degrees of obstruction at the pylorus resulting from the scar of perforation is of great importance in production of undesirable side effects.

Because high gastric acidity is of importance in peptic ulcer and because acid is secreted under 2 influences, 1 of which is blocked by the operation under discussion, the problem of the part played by the degree of preoperative gastric acidity arises. In this series it did not appear to be important insofar as the end result was concerned. There were relatively as many failures among those with normal or slightly increased acidity as there were in those with very high acidity. The level of immediate postoperative acidity appears to be of some value in predicting the outcome. Nine patients in the series had a gastric acidity after histamine ranging in the upper levels of normal, although in every case there was a significant drop from preoperative levels. Of the 9 there were 5 who experienced a return of ulcer symptoms. A percentage of 55.5 is difficult to ignore.

A number of authors have stated that there is no definite correlation between the insulin test and end results. In this series there were 6 instances of symptom recurrence severe enough to warrant further treatment among the group of 26 patients with definitely negative insulin responses. Thus the result in 23.2 percent of the patients could not have been predicted from the results of this test alone. Two patients had positive insulin tests; 1 had a good result and the other was a failure. The conversion of a previously negative to a positive insulin test during the follow-up period may have some prognostic significance. Three of our patients exhibited this change and all 3 had a recurrence of symptoms. Because vagotomy in most cases affects the amount of gastric secretion, the effect of a large volume of night secretion on the final outcome is interesting. The level of the preoperative volume apparently is of little importance as there were only 4 recurrences in a group of 16 patients with a night secretion volume above 1,000 cc. In view of the fact that there were 3 failures in 8 patients who had such a level *postoperatively*, this may also be an aid in prognosis.

The criteria for judging the completeness of vagotomy vary, but the following combination may be accepted: (1) a negative insulin test, (2) a fall in gastric acidity, and (3) a decrease in the volume of night secretion. In this series there were 21 patients in whom all 3 factors were present and adequately recorded yet 5 (23.8 percent) experienced a recurrence of ulcer. This would suggest that such a combination offers no greater prognostic assistance than the insulin test alone.

The presence of any evidence of obstruction is considered a contraindication to vagotomy alone. In this series there were 4 patients with minimal pyloric obstruction of whom 2 had poor results.

When do the greatest number of symptoms recur? From our series, indications are that the greatest number will recur in the early postoperative period. Twelve patients had a recurrence of symptoms; 7 in the first year; 3 in the second year; and 2 in the third year. No recurrences are known after 32 months. Study of the failures reveals that 4 of the 16 were due, not to ulcer recurrence, but to prolonged persistent side effects of a degree to be incapacitating, or to ulcer complications without the warning signs of pain or discomfort.

SUMMARY

In a series of 45 patients with peptic ulcer treated with vagotomy and followed for periods up to 60 months we observed that:

1. The immediate results of vagotomy were good in over 95 percent of the patients and relief of pain occurred almost at once. In about 70 percent of the patients the insulin test was negative, the gastric acidity and the volume of night secretion were significantly reduced. Ulcer healing occurred in almost all patients, but atony in varying degrees with gastric retention was present in about 60 percent.

2. Distressing side effects including diarrhea, distention, foul eructations, food intolerances, hypoglycemic-like episodes and post-incisional pain occurred and were troublesome and persistent in about 30 percent of the patients.

3. Subjective and objective results did not always correspond.

4. The age of the patient and duration of symptoms probably did not affect the end result.

5. The occurrence of previous complications of ulcer, particularly perforation, tended to influence late results unfavorably, probably by creating the proper conditions for obstruction.

6. There was a recurrence of symptoms in more than 50 percent of the patients who had a high postoperative acidity and a large volume of night secretion.

7. The insulin test was useful but could not be used to predict the final outcome.

8. The greatest number of symptoms recurred in the first postoperative year with a steady drop in rate thereafter.

9. Any degree of obstruction at the pylorus is a definite contraindication to the use of vagotomy alone.

10. Failures occurred in 35 percent of all patients and in about 40 percent of those treated by vagotomy alone.

11. Failure was due in about 25 percent of the patients to incapacitating side effects and not to ulcer recurrence.

12. There were no deaths attributable to the vagotomy.

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BOOK REVIEWS

Diabetes and Pregnancy, by *Ralph A. Reis,* B. S., M. D., F. A. C. S., Professor, Obstetrics and Gynecology, Northwestern University Medical School, Senior Attending Obstetrician and Gynecologist, Michael Reese Hospital; *Edwin J. DeCosta,* B. S., M. D., F. A. C. S., Assistant Professor, Obstetrics and Gynecology, Northwestern University Medical School, Associate Attending Obstetrician and Gynecologist, Michael Reese Hospital; and *M. David Allweiss,* B. S., M. D., Associate in Medicine, Northwestern University Medical School, Associate Attending, Department of Medicine, Michael Reese Hospital, Chicago, Ill. American Lecture Series Publication Number 158, A Monograph in American Lectures in Gynecology and Obstetrics. 78 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1952. Price $2.50.

In the preface the authors state that "there is much confusion concerning the problems and the management of the pregnant diabetic woman and her child," and in response to this challenge, these highly respected authors have given us a monograph that should prove valuable to all physicians who treat pregnant women. It is an unbiased presentation, is written clearly, and is easy to read. It has the charm of sounding as if the authors were in one's study informally discussing the subject. The authors have obtained their good results "by simple reasonable management of both the diabetes and the pregnancy." Each chapter is followed by a meaty summary. There is a bibliography of 78 well-chosen references.

—*Lt. Col. S. L. Avner, MC, U. S. A.*

Clinical Applications of Recreational Therapy, by *John Eisele Davis,* Sc. D., Chief, Corrective Therapy, The Veterans Administration, Washington, D. C. American Lecture Series Publication Number 123, A Monograph in American Lectures in Physical Medicine. 118 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1952. Price $3.75.

This monograph has been developed from the rich clinical experience in rehabilitation of the Veterans Administration. It attempts to present a scientific conception of recreation as an adjunctive therapy in modern psychiatric practice. The work further brings into sharper focus the concepts of recreation in its relationships to mental health. The book explores some of the recent developments in medical science in which physical exercise is a most important dynamic component of treatment. This book should prove of value to those interested in the use of various play and exercise forms as aids in medical treatment.

—*Lt. Col. R. C. Psaki, MC, U. S. A.*

Amputations and Recent Developments in Artificial Limbs

Thomas J. Canty, *Commander, MC, U. S. N. (1)*

AMPUTATIONS are among the oldest types of surgical operations, having been practiced in ancient times. Throughout the Middle Ages and up to the present the technics have been improved. At the Naval Amputation Center, since its inception in 1943, over 5,000 major operations have been performed without a single death due to amputations. This absence of mortality may be attributed to: (1) the use of vast quantities of whole blood, (2) administration of chemotherapeutic agents in large doses, (3) specialization in amputations, (4) early postoperative ambulation, and (5) most operations were performed on patients who were good surgical risks. On the other hand, many patients who were old or poor surgical risks underwent amputation.

Areas of election at particular levels of the extremity are becoming obsolete as improvements in prosthetic devices are developed. It may now be said in reference to amputations of the upper extremity: "Save as much as possible." In the lower extremity there remain but 2 areas unsuited for amputation: a zone in the tarsal region and a zone in the lower fourth of the tibia.

An emergency amputation is, as a rule, an open type of operation in which formal closure of the stump is not attempted. Guillotine and modified guillotine types of amputation should be condemned and, instead, the open flap type of amputation used. The open flap amputation as compared to the guillotine will save stump length, additional operations, and many weeks of morbidity.

All tissues in the distal part of the extremity which are beyond return to viability should be trimmed off, saving all viable skin, muscle, and bone. The skin is the principal factor determining length because if there is not sufficient skin to cover the bone and muscle, bone length must be sacrificed.

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Preoperative conditioning of a patient requiring emergency amputation is of prime importance. Shock must be combated by adequate replacement of lost blood. Chemotherapeutic agents should be used in tremendous doses and the anesthetic carefully chosen.

Associated injuries, such as severe head or chest wounds, should take precedence over a gangrenous extremity in the treatment. A tourniquet can be placed on the extremity at the proximal end of the damaged part and the extremity packed in ice until the associated injuries are under control.

A patient with gas gangrene in an extremity can also be treated with a tourniquet, an ice pack, tremendous doses of chemotherapeutic agents, and blood transfusions administered prior to the amputation. The amputation may be performed in the bed, without additional anesthesia and with slight loss of blood, provided an additional pneumatic tourniquet is used.

In addition to preoperative administration, whole blood should be given during the amputation and postoperatively as necessary. It is far better to administer 1,000 or 2,000 cc. of blood prior to and during the operation to prevent shock than to use heroic measures after shock has ensued. An elective operation allows adequate time for careful preoperative care. The blood volume can be brought up to normal by whole blood transfusions. Associated diabetic and cardiac conditions can be stabilized. The choice of anesthetic and the site of amputation can be carefully planned and the patient can be prepared psychologically.

Because of technical advances in artificial limbs, the length and muscular power of a stump is becoming increasingly important and surgeons should plan to allow as much stump length as possible. Skin flaps should be planned to provide the operative scar at the middle and posterior third on the end of the stump. If the remaining viable tissues will not permit, the scar should be placed in any position in order to save length. The skin flaps may be drawn on the skin by means of gentian violet prior to incision. A pneumatic tourniquet is generally used except on patients with a deficient circulatory tree, such as those with thromboangiitis obliterans.

The skin is incised down to the muscle fascia and the flaps then reflected back on themselves by blunt dissection in the line of cleavage. Muscles are amputated at a slightly higher level down to the bone. The main blood vessels are clamped with large hemostats. If no tourniquet is used, the surgeon has about 30 seconds in which to clamp off the main vessels before the patient would bleed to death. When a tourniquet is not used, it is better carefully to dissect out the main vessels and clamp them proximally prior to cutting. The muscle attachment on the bone is carefully dissected proximally without stripping the periosteum from the bone. At the desired height, the periosteum is incised circularly and the distal part stripped down.

The bone is then sawed through at the periosteal incision and the amputated extremity discarded. Minor bleeding points are clamped. All major vessels are isolated, ligated, and then transfixed and ligated below the first tie. With small vessels in a muscle mass, a figure-8 tie may be used.

The nerves are carefully located, pulled down in their sheath as far as possible, amputated with a clean through incision at the highest point possible, and then allowed to retract. This method of treating nerve ends helps to prevent the formation of painful neuromas. If a neuroma becomes attached to scar tissue, which in turn is attached to bone, muscle, or the skin, the constant stress which occurs on the neuroma causes a bombardment of stimuli with every motion of the stump. A reflex reaction and habit pattern ensues and the amputee may be seriously troubled with phantom pain.

Bone ends are beveled and filed to give them smooth ends. In the lower part of the leg, the tibia is beveled anteriorly and the fibula amputated about 1 inch shorter than the tibia and beveled on the side. This method of treating the bone ends is used because: (1) it permits a more desirable conically shaped stump; (2) it seldom results in a ring sequestrum and aseptic necrosis of the bone end; and (3) it results in less osteoma and spur formation. There are 2 principal factors in spur formation: (1) tissue memory and nature's attempt to regrow the lost part and (2) stress resulting from new muscular attachments on the bone. Nature lays down new bone in order to compensate for the forces applied by muscular action.

When the bone ends are smooth the tourniquet, if used, is released in order to find bleeding points. Small bleeders may be controlled with electrocoagulation. A bleeding bone and/or mass of oozing can be controlled by an absorbable sponge. Hemostasis must be as complete as possible. Drains are seldom used.

The main muscle groups are sutured to each other. The adductors in the thigh are sutured to the adjacent structures. The skin flaps are sutured together with buried chromic catgut. The skin is closed by careful apposition with nonabsorbable sutures. Only absorbable sutures should be used in the stump, as nonabsorbable sutures are often a source of trouble later. Postoperatively, petrolatum gauze secured by an elastic bandage is used over the closed incision.

If his general condition permits, the patient is allowed up in a wheel chair the second day. Sutures are removed in from 7 to 10 days and the stump is then shrunk by means of a heavy elastic bandage. The amputee is fitted with a prosthesis as soon as the wound is healed.

When it is necessary to amputate the foot the Syme's amputation is preferred. The main advantage of the Syme's stump, besides its length, is that it permits the amputee to walk on the stump directly, without a

prosthesis, in case of an emergency. The disadvantages are fitting problems and the minimal space available for the ankle joint below the stump. In the femur the Gritti-Stokes amputation is preferred. Its advantage is a long, powerful stump with anatomic quadriceps muscle attachment through the patella. The patient can use end-bearing and he also can be fitted with a suction socket. The disadvantage is the minimal space available for the knee joint. When a thigh amputation is complicated by a fracture of the femur in the stump, the treatment of choice is open reduction and intramedullary nailing. This permits early ambulation of the patient and early fitting with a prosthesis.

Because of improvement in fitting and the use of the soft socket, stumps that are badly scarred or which have had skin grafts are better able to tolerate an artificial leg. Scarred stumps often may be improved by plastic surgery. The percent of successful takes of skin grafts is directly proportional to the blood supply of the granulating wound and the control of local infection. Chemotherapy, both systemic and local, helps to overcome the infection. A granulating area which has a poor blood supply and chronic, low grade, persistent infection is often stimulated by erythema doses of ultraviolet light applied directly. This is administered 3 or 4 times, every other day. The donor area should always be selected from the nonaffected limb or the abdomen. The split-thickness skin graft should be fairly thin, perforated for drainage, and sutured to the recipient area. Postoperatively the wound is left exposed to the air without pressure dressings. The graft should be rolled with a swab dipped in sterile saline solution every few hours for the first few days in order to remove the exudate which has a tendency to collect and separate the graft from its bed. The exudate can drain through the perforations in the graft. It is not unusual to get a high percent of takes with this method.

Cineplastic operations are used for amputations of the upper extremity and a large number of forearm cineplastic motors have been provided in the past. At present the biceps motor is preferable for amputations below and a pectoralis motor for those above the elbow. Biceps and pectoralis motors supply excursions of from 2½ to 4 inches and develop from 40 to 80 pounds pulling force. These are adequate for the operation of terminal appliances. Bilateral arm amputees can use cineplastic motors to great advantage. The advantages of a biceps motor in amputations below the elbow are: (1) It permits more precision with the use of the hook or the hand, giving the amputee instant neuromuscular control of his terminal device at all times; (2) no shoulder harness is necessary and all shoulder motions are used for their natural functions; and (3) the amputee may operate his terminal device in any position in which he is able to place his extremity (not possible with the shoulder harness type).

At the Naval Amputation Center the treatment of amputees includes a well-rounded rehabilitation program which consists of: (1) adequate

medical and surgical care, (2) physical reconditioning of the body and stump, (3) provision with a modern, comfortable prosthesis, (4) training in the use of the prosthesis, (5) prevocational and educational services, (6) psychologic aids and helps to the handicapped, and (7) selective job placement. Follow-up records reveal that about 95 percent of the amputees who have been discharged from the Center have been successfully rehabilitated. They have made a satisfactory social adjustment in their respective communities and are gainfully employed in almost every type of occupation.

Research and developmental work on artificial limbs is difficult and time-consuming. The neuromuscular and mechanical features with which nature has provided us are truly the acme of mechanical genius and we can only hope to provide a poor substitute with very limited functions. A successful prosthetic device must be simple; it must function in a manner similar to that of the part it replaces; it must be fitted properly in order that the amputee can wear it without discomfort; and it must be light, strong, durable, economical, and cosmetically acceptable.

The following newly developed prostheses are at present being furnished our Korean amputee casualties:

An *above-the-knee suction socket.* About 90 percent of all above-the-knee amputees at this center are fitted with suction sockets. Use of the suction socket eliminates the heavy and uncomfortable waist belt which is ordinarily attached through a hip hinge to the socket. Many patients who have lost a limb or limbs through alterations in the blood supply, such as those with thromboangiitis obliterans, find the suction socket to be particularly beneficial. The slight alternating positive and negative pressures encountered in wearing the suction socket actually serve as a sort of built-in pavex boot.

A *below-the-knee soft socket* has been in routine use here for several years. Follow-up studies and interviews with numerous patients over a period of many months indicate this to be a substantial improvement. Although the most important feature of this device lies in its comfort for the patient, the anatomic and physiologic advantages gained by its use should not be minimized.

A *below-the-knee* suction socket. A number of below-the-knee amputees have been fitted with the soft socket which is retained on the stump by means of the suction socket principle.

A *plastic shin.* The first production type of plastic shank was produced by this department in 1943. Two important changes have been made in it since then. Improved materials now allow efficient and rapid production of a shin which is both lighter and stronger than the original. Based on anthropomorphic studies conducted at the University of California, the shape of the shin now closely approaches that of

most amputees. In patients in whom a marked divergence from standard measurements exists, it is a simple matter to alter the shape so that the desired conformation is secured.

A *cosmetic cover.* Experimental cosmetic covers are being made for a small number of female amputees. These closely simulate the appearance, color, texture, and feel of human skin and therefore allow the wearing of sheer hose. Furthermore, the surface which is colored to match the opposing member may now be more accurately matched throughout the various seasons by the patient herself with "pancake" makeup.

An *above-the-elbow Navy-Fitch forearm.* This device was the first prosthesis developed in World War II to become commercially available. It depends on the anterior or posterior motion of the stump to flex or to extend the mechanical elbow. This motion is secured by anchoring a flexible steel cable to the forward edge of the harness saddle, allowing it to pass around a pulley on the elbow axis and attaching it to the posterior surface of the saddle. The forearm is at all times under positioning control by the wearer and produces quite lifelike motions. Experimentally, suction sockets have been successfully used with this prosthesis. The Navy-Fitch arm is available at reasonable prices at all artificial limb shops.

A *below-the-elbow plastic forearm.* In below-the-elbow prostheses flexibility is secured through the use of elbow hinges and a small, open, biceps cuff which is comfortable and allows great freedom and quite heavy manual labor by the patient.

A *below-the-elbow cineplastic forearm.* A number of below-the-elbow amputees have been provided with biceps cineplastic motors used to actuate the hook or hand. The elimination of much of the conventional harness through the use of these motors constitutes an important achievement. The neuromuscular control of the hook or hand is a substantial step toward replacing the original function of the lost hand.

A *mechanical hand and cosmetic glove.* Much work has been devoted to producing an artificial hand and glove which would be interchangeable with the conventional hook so that arm amputees might have a device for social use. This articulated hand is at present undergoing final redesign, on completion of which it is planned to fabricate suitable dies for limited mass production. The latest addition to the device is an alternating lock whereby the wearer may grasp and hold an object without conscious effort. Each plastic glove, designed to cover the mechanical member, is individually colored during fabrication to simulate as closely as possible the coloration of the patient's remaining hand. The mechanical component weighs about 10 oz. and is quickly interchangeable with the hook, no further adjustments being necessary in the harness or actuating cable.

Treatment of Acute Rheumatic Fever With ACTH

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IN the past 2 years, many workers have reported beneficial effects of ACTH and cortisone therapy in patients with acute rheumatic fever (2-10). The importance of these findings led to the use of ACTH in the treatment of 30 patients with acute rheumatic fever seen at this hospital. Thorn et al. (11) and Massell et al. (5) administered 10 mg. of ACTH intramuscularly every 6 hours for from 10 days to

(1) United States Air Force Hospital, Lowry Air Force Base, Denver, Colo.

(2) Hench, P. S.; Slocumb, C. H.; Barnes, A. R.; Smith, H. L.; Polley, H. F.; and Kendall, E. C.: Effects of adrenal cortical hormone 17-hydroxy-11-dehydrocorticosterone (compound E) on acute phase of rheumatic fever; preliminary report. Proc. Staff Meet., Mayo Clin. 24: 277-297, May 25, 1949.

(3) Hench, P. S.; Slocumb, C. H.; Polley, H. F.; and Kendall, E. C.: Effect of cortisone and pituitary adrenocorticotropic hormone (ACTH) on rheumatic diseases. J. A. M. A. 144: 1327-1335, Dec. 16, 1950.

(4) Wilson, M. G., and Helper, H. N.: Effect of pituitary adrenocorticotropic hormone (ACTH) in acute rheumatic carditis. J. A. M. A. 145: 133-138, Jan. 20, 1951.

(5) Massell, B. F.; Warren, J. E.; and Sturgis, G. P.: Observations on effects of ACTH in patients with rheumatic fever and rheumatic carditis. Paper No. 32. In Mote, J. R. (editor): Proceedings of the First Clinical ACTH Conference. The Blakiston Co., Philadelphia, Pa., 1950. pp. 405-418.

(6) Massell, B. F.; Warren, J. E.; Sturgis, G. P.; Hall, B.; and Craige, E.: Clinical response of rheumatic fever and acute carditis to ACTH. New England J. Med. 242: 641-647, Apr. 27; 692-698, May 4, 1950.

(7) Massell, B. F.: Symposium on specific methods of treatment; salicylates, hormones and penicillin in treatment of rheumatic fever. M. Clin. North America 34: 1419-1434, Sept. 1950.

(8) Massell, B. F., and Warren, J. E.: Effect of pituitary adrenocorticotropic hormone (ACTH) on rheumatic fever and rheumatic carditis. J. A. M. A. 144: 1335-1341, Dec. 16, 1950.

(9) Barnes, A. R., and Smith, H. L.: Effects of administration of cortisone and ACTH on patients with acute rheumatic fever. Mod. Concepts Cardiovas. Dis. 19: 59-60, Feb. 1950.

(10) Harris, T. N.; Abrams, W. B.; Leo, T. F. P.; and Hubbard, J. P.: Cortisone therapy in acute rheumatic carditis; preliminary observations. Circulation 3: 215-223, Feb. 1951.

(11) Thorn, G. W., et al.: Medical progress; studies on relation of pituitary-adrenal function in rheumatic disease. New England J. Med. 241: 529-537, Oct. 6, 1949; correction 241: 1057, Dec. 29, 1949.

several weeks. Because the resolution of symptoms on this dosage proved unsatisfactory in our series we gave most of our patients larger doses. Adams and Dwan *(12)* reported that the sedimentation rate and the hyaluronidase inhibitor level dropped in from 10 to 15 days in the patients with acute rheumatic fever treated with ACTH or cortisone. The serum mucoproteins, however, returned to normal levels much more slowly. If ACTH or cortisone were withdrawn before a substantial drop of the mucoprotein level had taken place, the patient always suffered a recurrence of the disease. It was therefore decided that all patients in this series would receive therapy for a total of 6 weeks, this being considered ample time for the laboratory and clinical findings to return to normal.

Sayers et al. *(13)* described the fate and metabolic effects of ACTH given intravenously. Gordon *(14)* demonstrated a twentyfold increase in response to ACTH when a given dose was administered intravenously during a 12-hour period as compared with the administration of the same amount by a single intramuscular injection. Because the hormone is inactivated by muscle enzymes *(15)*, we gave ACTH intravenously for the first week in the last 14 patients in this series. Although recent articles have discussed the use of ACTH intravenously in normal persons and in patients with various disease states, no reference to its use in acute rheumatic fever has been reported *(16, 17)*. Our patients have been followed for periods of from 1 to 12 weeks following the 6-week course of hormone therapy.

MATERIAL AND METHODS

Thirty patients with acute rheumatic fever were treated with ACTH. The diagnostic criteria as set forth by the American Council for Rheumatic Fever of the American Heart Association were used. Patients with borderline manifestations were excluded. The investigation prior to therapy included history, physical examination, ECG, teleroentgenograms, hemogram, sedimentation rate (Wintrobe, corrected by the Whitby and Hines chart, to a hematocrit of 45 percent), daily throat cultures for 3 days, daily blood cultures for 4 days, urinalysis, serologic tests, and blood nonprotein nitrogen, calcium, phosphorus,

(12) Adams, F. H. (Minneapolis), and Dwan, P. F.: Cortisone and ACTH in rheumatic fever. Journal-Lancet 70: 389-390, Oct. 1950.

(13) Sayers, G.; Burns, T. W.; Tyler, F. H.; Jager, B. V.; Schwartz, T. B.; Smith, E. L.; Samuels, L. T.; and Davenport, H. W.: Metabolic actions and fate of intravenously administered adrenocorticotropic hormone in man. J. Clin. Endocrinol. 9: 593-614, July 1949.

(14) Gordon, E. S.: Adrenal stimulation by intravenous ACTH. (Abstract) J. Lab. & Clin. Med. 36: 827-828, Nov. 1950.

(15) Li, C. H.: Adrenocorticotropin (adrenocorticotropic hormone, ACTH). Nord. Med. 43: 363-366, Mar. 3, 1950.

(16) Mandel, W.; Singer, M. J.; Gudmundson, H. R.; and Meister, L.: Intravenous use of pituitary adrenocorticotropic hormone (ACTH); report on its administration in 25 patients. J. A. M. A. 146: 546-551, June 9, 1951.

(17) Renold, A. E.; Forsham, P. H.; Maisterrena, J.; and Thorn, G. W.: Intravenously administered ACTH. New England J. Med. 244: 796-798, May 24, 1951.

sugar, and carbon dioxide levels. On admission, all patients were placed on complete bed rest, being allowed up only to be taken to the bathroom, in a wheel chair, for bowel movements. Bed rest was continued throughout the period of therapy and thereafter until the sedimentation rate returned to normal and no signs or symptoms of acute rheumatic fever were present.

Therapy was instituted within 6 days after the onset of acute symptoms. In the initial group of 16 patients who were given ACTH intramuscularly, no rigid dosage pattern was followed. An attempt was made to give the hormone in amounts to meet the symptomatic needs of the patient. The hormone was given in equally divided doses every 6 hours. In the first 2 patients 40 mg. of ACTH was given intramuscularly every day. Because the resolution of symptoms at this level was not satisfactory, the next 6 patients were given 80 mg. a day in the first week and the dose was gradually reduced (in a 6-week period) to 40 mg. a day in the last week. In 5 of these (patients 3, 5, 6, 7, and 16), larger doses were necessary because of persistence or recurrence of symptoms. Eight patients were given 100 mg. of ACTH a day initially (patients 8 and 9 for 1 week and patients 10 to 13 for 2 weeks). More than 100 mg. daily was necessary to control the symptoms in patients 14 and 15.

Because of the failure to relieve symptoms with larger doses of ACTH by the intramuscular route in several of the patients seen early in the study, a program using ACTH intravenously was instituted. In patients 17 to 30 ACTH was administered intravenously during the first week; 25 mg. of the hormone in 1,000 cc. of 5 percent dextrose solution was given in a 12-hour period for the first 3 days and in an 8-hour period for the next 4 days. Thereafter, treatment was given intramuscularly as follows: 100 mg. daily for 1 week; 80 mg. daily for 2 weeks; 60 mg. daily for 1 week; and 40 mg. daily for 1 week. In patient 29, because of a recurrence of symptoms, the fourth week of therapy consisted of 140 mg. rather than 80 mg. of ACTH intramuscularly every day. Patient 30 was given 140 mg. instead of 80 mg. of ACTH daily during the third week of therapy because of a recurrence of symptoms. When no relief was obtained during a 48-hour period, another 7-day course of ACTH was given intravenously. After 33 days of the intramuscular administration of ACTH, patient 16 was given a 4-day course of ACTH intravenously because of progression of carditis. The ACTH was discontinued prior to death.

Throughout the course of ACTH therapy, the patients were given a low salt diet (700 mg. per day) and 3 grams of potassium chloride in solution daily by mouth. All patients received 300,000 units of penicillin G procaine in aluminum monostearate intramuscularly twice weekly throughout the 6-week course of ACTH therapy.

The observation of each patient included careful daily recording of the temperature, pulse, respirations, weight, blood pressure, heart

murmurs, joint symptoms, skin and mental changes, and the presence of edema. ECG's (standard limb and unipolar leads) were taken every other day for 1 week and every 5 days thereafter until 3 weeks after discontinuance of ACTH therapy when they were taken every 10 days. Roentgenograms of the chest were taken every 10 days if cardiac enlargement was noted and in all patients at the end of the course of therapy. The sedimentation rates were taken every other day during the first week and every 5 days thereafter. A leukocyte count, urinalysis, and fasting blood sugar were also taken every 5 days. Blood calcium, phosphorus, carbon dioxide, and nonprotein nitrogen determinations were made at 30-day intervals.

OBSERVATIONS

All 30 patients were white men ranging in age from 18 to 27 years. Eight had a definite family history of acute rheumatic fever and 2 of these had previous episodes themselves. The patients had resided in all parts of the United States, only 1 having originally come from the Rocky Mountain area. All but 2 had been stationed at Lackland Air Force Base, San Antonio, Tex., prior to coming to Denver. Fourteen patients noted symptoms of acute rheumatic fever within 1 month after arrival at this base. The remainder developed the disease within 5 months after arrival.

All but 2 patients had heart murmurs prior to ACTH therapy. In 19, the murmur was mitral systolic in type; in 7 it was both aortic and mitral systolic. One (patient 24) had aortic diastolic and mitral presystolic murmurs in addition to the systolic murmurs. His heart showed a 20 percent enlargement. Patient 7 exhibited definite prominence of the pulmonary segment, a 15 percent enlargement in heart size and an electrocardiographic pattern of acute pericarditis. In only 1 patient were dyspnea and orthopnea noted prior to hormone therapy. Arthritis in 2 or more joints was exhibited in all patients in this series except 1 who had pain only in the left shoulder. Erythema marginatum was present in 2 patients. Chorea and subcutaneous nodules were not noted in this series.

All patients showed an elevated sedimentation rate and a pharyngitis sometime during the month prior to the acute illness. All but 2 had fever. Twelve patients had received penicillin therapy for acute pharyngitis prior to the onset of symptoms of acute rheumatic fever. A P-R interval of 0.21 or more seconds was present in 14 patients prior to therapy. Two of these exhibited the Wenckebach phenomenon. Another (patient 18) with a normal P-R interval had a 2:1 heart block. Eight patients had had previous episodes of acute rheumatic fever. These observations are summarized in table 1.

ACTH therapy produced rapid initial effects on the nonspecific signs and symptoms of acute rheumatic fever. High temperatures returned to normal within 72 hours after the start of therapy intramuscularly in all

except patient 15 who required 27 days. In all the patients initially treated intravenously, clearance of the fever occurred within 24 hours except for 1 who required 48 hours. Fever subsided prior to treatment on bed rest alone in 8 patients. The heart rate returned to normal in 14 patients on bed rest. In the rest initially treated intramuscularly, a normal heart rate resulted in from 1 to 4 days except again in patient 15, in whom it took 27 days. In the intravenously treated patients, a normal rate was noted in from 24 to 48 hours. A sense of well-being resulted in most patients within 48 hours after the start of therapy. Following an initial weight loss, good appetite returned after 1 or 2 weeks on ACTH therapy with a resultant weight gain. A gradual rise in hemoglobin occurred. The sedimentation rate remained elevated for from 1 to 87 days. In 6 patients the rate required 26 or more days to return to normal. The rate returned to normal more rapidly (from 2 to 19 days) in the patients treated intravenously as compared with those treated intramuscularly.

The positive antirheumatic changes noted after the start of ACTH therapy were improvement in the quality of heart sounds and subsidence of polyarthritis. In the patients treated intramuscularly, a clearance of the joint symptoms took from 4 to 7 days and in the 2 patients requiring larger doses, 16 and 27 days respectively. In 8 of the first 16 patients in this series, the polyarthritis cleared on bed rest alone. In patients 17 to 30, treated intravenously, clearance occurred in from 1 to 3 days with 2 exceptions, 1 having cleared prior to therapy and the other requiring 6 days.

Favorable changes in the carditis following a course of ACTH were questionable as judged mainly by the presence of or changes in murmurs, abnormal heart contour, and electrocardiographic patterns. In 20 patients, a mitral systolic murmur of varying intensity persisted. In 6, there was a disappearance of this murmur. After 3 weeks of hormone therapy 1 (patient 2) developed a mitral systolic murmur which has persisted. An aortic systolic murmur failed to clear after therapy and during the follow-up period in 8 patients. In only 2 did the aortic systolic murmur disappear on therapy. The aortic and mitral diastolic murmurs which were present in patient 24 persisted following therapy. A mitral diastolic murmur developed on the second day of ACTH therapy in patient 15 and persisted thereafter. In 1 (patient 4), a double mitral murmur developed during therapy but disappeared after several days.

Of the 14 patients with prolonged P-R intervals, 1 (patient 29) cleared on bed rest alone prior to hormone therapy. In 4 of the patients treated with the drug intramuscularly this electrocardiographic abnormality cleared in from 5 to 11 days. In 1 of these (patient 8) the P-R interval returned to normal in 7 days, but again became abnormal 1 month after therapy had been instituted. It again became normal after 7 days' treatment with 100 mg. of ACTH given intramuscularly every day. In 3

TABLE 1. *Summary of signs and symptoms prior to ACTH therapy*

Patient	Major manifestations						Minor manifestations				
	Carditis				Poly-arthritis	Erythema margin-atum	Fever	Sedimen-tation rate above 15 mm.	History of pharyn-gitis in past month	Increased P-R interval	Previous history of rheumatic fever
	Murmurs	Increased heart size	Peri-carditis	Dyspnea and orthopnea							
1	+	-	-	-	+	-	+	+	+	+	-
2	-	-	-	-	+	-	+	+	+	-	-
3	+	-	-	-	-	-	-	+	+	+	+
4	+	-	-	-	+	-	+	+	+	-	+
5	+	-	-	-	+	-	+	+	+	-	-
6	-	-	-	-	+	-	+	+	+	+	-
7	+	-	+	-	+	-	+	+	+	+	-
8	+	-	-	-	+	-	-	+	+	+	+
9	+	-	-	-	+	-	+	+	+	+	-
10	+	-	-	-	+	-	+	+	+	-	-
11	+	-	-	-	+	-	+	+	+	-	-
12	+	-	-	-	+	-	+	+	+	-	-
13	+	-	-	-	+	-	+	+	+	-	-
14	+	-	-	-	+	-	+	+	+	-	+
15	-	-	-	-	+	-	+	+	+	+	-

TABLE 1. *Summary of signs and symptoms prior to ACTH therapy*—Continued

Patient	Major manifestations						Minor manifestations				
	Carditis				Poly-arthritis	Erythema margin-atum	Fever	Sedimen-tation rate above 15 mm.	History of pharyn-gitis in past month	Increased P-R interval	Previous history of rheumatic fever
	Murmurs	Increased heart size	Peri-carditis	Dyspnea and orthopnea							
16	+	-	-	-	+	-	+	+	+	+	+
17	+	-	-	-	+	-	+	+	+	+	-
18	+	-	-	-	+	-	+	+	+	+	-
19	+	-	-	-	+	-	+	+	+	-	+
20	+	-	-	-	+	-	+	+	+	-	-
21	+	-	-	-	+	-	+	+	+	-	-
22	+	-	-	-	+	-	+	+	+	+	+
23	+	-	-	-	+	-	+	+	+	-	-
24	+	+	-	-	+	-	+	+	+	-	+
25	+	-	-	+	+	+	+	+	+	-	-
26	+	-	-	-	+	-	+	+	+	-	-
27	+	-	-	-	+	-	+	+	+	+	-
28	+	-	-	-	+	+	+	+	+	+	-
29	+	-	-	-	+	-	+	+	+	+	-
30	+	-	-	-	+	-	+	+	+	-	-

of the intramuscularly treated patients the P-R interval required from 23 to 65 days to return to normal. One (patient 16) who had received ACTH for 37 days continued to have a prolonged P-R interval until he died. In the 5 patients treated with ACTH intravenously and in whom the P-R interval was prolonged, a return to normal took place in from 4 to 11 days after the start of therapy. Patient 23 first developed a prolonged P-R interval on the fourth day of therapy. It lasted 6 days. On the twenty-third day of his treatment an abnormal interval was again noted. It also lasted 6 days. Following the 6-week course of ACTH a prolonged P-R interval resulted for the third time, subsiding 22 days later. One (patient 7) developed an electrocardiographic pattern of acute pericarditis just prior to the start of intramuscular treatment with ACTH. This persisted for 7 weeks. Following the initial week of intravenous therapy with ACTH, patient 21 developed the electrocardiographic changes of acute pericarditis which cleared 3 weeks later while the patient was receiving hormone therapy. In 1 (patient 18) a 2:1 heart block disappeared after the termination of a 6-week course of ACTH.

Only 2 patients had roentgenographic evidence of enlargement of the heart. Patient 24, who had a 20 percent enlargement before therapy, showed an increase to 25 percent during treatment and throughout the follow-up period. In 1 (patient 7), the heart size decreased from 15 percent to 8 percent enlargement during therapy. An exacerbation on the thirty-ninth day after treatment was discontinued resulted in more than 25 percent enlargement. This responded dramatically to a second course of ACTH, this time given intravenously.

The erythema marginatum which was present in patient 25, began clearing prior to hormone therapy and was completely absent 48 hours after treatment with ACTH had been started. A second patient with this lesion cleared within 24 hours after therapy was started.

A recurrence of symptoms during the course of ACTH therapy was noted in 11 patients; 8 were in the group treated only by the intramuscular route. A remission of symptoms followed an increase in the dose of ACTH in 9 patients; the other 2 cleared without any change in the dosage.

In 6 of the first 16 patients, treated intramuscularly, a recurrence of symptoms developed from 2 to 14 days after the 6-week course of ACTH was completed. The symptoms varied in each patient and consisted of polyarthritis, fever, tachycardia, and an increased sedimentation rate. A spontaneous remission was noted in 5 of the 6 patients in from 1 to 7 days. Patient 7 had an exacerbation of the disease 39 days after the 6-week course of ACTH was completed and required further hormone therapy. In the group treated intravenously, an exacerbation in from 1 to 8 days following therapy occurred in 8 patients. Symptoms disappeared spontaneously in from 2 to 15 days. In all patients with a return of symptoms, the sedimentation rate remained elevated for periods up to 3 weeks.

The side effects of hormone therapy included folliculitis which occurred in 2 of the patients treated intramuscularly and in 11 of those treated intravenously. Moonface was exhibited by 7 of those treated intramuscularly and by 9 of those treated intravenously (fig. 1). Adiposity ("potbelly") was noted in 8 of those treated intravenously; strias were present in 1 (patient 25). No electrolyte imbalance was noted. An erythematous rash over the trunk appeared in 2 patients

Figure 1. Severe folliculitis and moonface as noted during the sixth week of ACTH therapy in patient 28.

during the course of therapy and disappeared in from 1 to 5 days. Two patients developed urticarial lesions during their 6-week course of hormone therapy. In 1 it persisted even after discontinuance of ACTH. This urticaria may have been a result of a sensitivity either to penicillin or to the porcine ACTH extract. One patient became disoriented while on hormone therapy, but was normal on the following morning. The results of treatment are summarized in table 2.

DISCUSSION

The data presented here does not warrant drawing definite conclusions on the value of ACTH in the treatment of acute rheumatic fever, especially with respect to its value in dispelling the signs and symptoms of rheumatic carditis. Certain general conclusions, however, appear to be justified at this time.

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TABLE 2. *Summary of results and changes with ACTH therapy*

Patient	Dosage in mg.	Folliculitis	Moon-face	Number of days to return to normal					Persistence of murmurs following ACTH therapy	Recurrence of symptoms	
				Fever	Pulse*	Polyarthritis	P-R interval	Sedimentation rate		During ACTH therapy	Following ACTH therapy
1	40 IM daily for 1 wk. 80 IM daily for 4 days 60 IM daily for 1 wk. 40 IM daily for 24 days	-	-	0	0	0	10	87	+	+	-
2	40 IM daily for 4 days 80 IM daily for 1 wk. 60 IM daily for 1 wk. 40 IM daily for 1 wk. 80 IM daily for 12 days 60 IM daily for 5 days	-	-	0	0	7	x	35	+	+	-
3	80 IM daily for 1 wk. 60 IM daily for 1 wk. 40 IM daily for 3 wk. 100 IM daily for 10 days	-	+	x	x	x	65	26	+	-	-
4	80 IM daily for 32 days 60 IM daily for 10 days	-	+	2	0	0	x	60	+	-	+
5	80 IM daily for 1 wk. 100 IM daily for 9 days 80 IM daily for 2 wk. 60 IM daily for 12 days	-	+	2	0	0	x	7	+	-	-

TABLE 2. *Summary of results and changes with ACTH therapy*—Continued

Patient	Dosage in mg.	Follicu-litis	Moon-face	Number of days to return to normal					Persist-ence of murmurs follow-ing ACTH therapy	Recurrence of symptoms	
				Fever	Pulse*	Poly-arthri-tis	P-R in-terval	Sedi-menta-tion rate		During ACTH therapy	Following ACTH therapy
6	80 IM daily for 4 days 100 IM daily for 1 wk. 80 IM daily for 10 days 60 IM daily for 1 wk. 40 IM daily for 2 wk.	-	-	3	3	7	11	1	-	+	-
7	80 IM daily for 9 days 60 IM daily for 5 days 100 IM daily for 6 days 140 IM daily for 4 days 200 IM daily for 3 days 160 IM daily for 3 days 120 IM daily for 7 days 100 IM daily for 5 days	+	-	2	2	5	7	5	+	+	+
8	100 IM daily for 1 wk. 80 IM daily for 2 wk. 60 IM daily for 2 wk. 40 IM daily for 1 wk.	-	-	x	x	0	7	17	+	-	-
9	Same dosage as patient 8	-	-	0	1	0	5	10	+	+	+

TABLE 2. *Summary of results and changes with ACTH therapy*—Continued

Patient	Dosage in mg.	Folliculitis	Moon-face	Number of days to return to normal					Persistence of murmurs following ACTH therapy	Recurrence of symptoms	
				Fever	Pulse*	Poly-arthritis	P-R interval	Sedimentation rate		During ACTH therapy	Following ACTH therapy
10	100 IM daily for 2 wk. 80 IM daily for 1 wk. 60 IM daily for 2 wk. 40 IM daily for 1 wk.	-	-	3	4	4	x	12	+	-	-
11	Same dosage as patient 10	+	+	2	2	4	x	12	-	-	+
12	Same dosage as patient 10	-	-	0	0	0	x	15	-	-	-
13	Same dosage as patient 10	-	-	0	0	0	x	0	-	-	-
14	100 IM daily for 6 days 80 IM daily for 5 days 100 IM daily for 12 days 140 IM daily for 11 days 100 IM daily for 5 days 60 IM daily for 3 days	-	+	1	0	16	x	34	+	+	+
15	100 IM daily for 6 days 120 IM daily for 7 days 100 IM daily for 2 days 120 IM daily for 8 days 200 IM daily for 5 days 180 IM daily for 2 days 160 IM daily for 4 days 120 IM daily for 8 days	-	+	27	27	27	23	45	+	+	-

TABLE 2. *Summary of results and changes with ACTH therapy*—Continued

Patient	Dosage in mg.	Follicu-litis	Moon-face	Number of days to return to normal					Persist-ence of murmurs follow-ing ACTH therapy	Recurrence of symptoms	
				Fever	Pulse*	Poly-arthri-tis	P-R in-terval	Sedi-menta-tion rate		During ACTH therapy	Following ACTH therapy
16	80 IM daily for 10 days 60 IM daily for 3 days 100 IM daily for 20 days 25 IV daily for 4 days	-	+	0	0	0	R	8	+	+	Died
17	25 IV daily for 1 wk. 100 IM daily for 1 wk. 80 IM daily for 2 wk. 60 IM daily for 1 wk. 40 IM daily for 1 wk.	+	+	0	0	2	5	9	+	+	-
18	Same dosage as patient 17	+	+	1	0	2	9	19	+	-	+
19	Same dosage as patient 17	+	+	1	0	2	x	7	+	-	+
20	Same dosage as patient 17	-	+	1	1	3	x	9	+	-	-
21	Same dosage as patient 17	+	+	1	2	3	x	11	-	-	+
22	Same dosage as patient 17	-	-	1	0	1	4	2	+	-	-
23	Same dosage as patient 17	+	-	1	0	2	x**	11	+	-	+

TABLE 2. *Summary of results and changes with ACTH therapy*—Continued

Patient	Dosage in mg.	Follicu-litis	Moon-face	Number of days to return to normal					Persist-ence of murmurs follow-ing ACTH therapy	Recurrence of symptoms	
				Fever	Pulse*	Poly-arthri-tis	P-R in-terval	Sedi-menta-tion rate		During ACTH therapy	Following ACTH therapy
24	Same dosage as patient 17	+	+	1	1	3	x	9	+	-	-
25	Same dosage as patient 17	-	-	1	2	6	x	9	-	-	-
26	Same dosage as patient 17	+	+	1	1	2	x	6	+	-	+
27	Same dosage as patient 17	+	+	0	0	0	11	6	+	-	+
28	Same dosage as patient 17	+	+	1	2	2	9	13	+	-	+
29	25 IV daily for 1 wk. 100 IM daily for 1 wk. 80 IM daily for 2 wk. 140 IM daily for 9 days 60 IM daily for 5 days	+	-	1	0	1	0	5	-	+	+
30	25 IV daily for 1 wk. 100 IM daily for 4 days 140 IM daily for 2 days 25 IV daily for 1 wk. 100 IM daily for 1 wk. 80 IM daily for 15 days	+	-	2	1	3	x	8	+	+	-

0 Indicates clearance of sign or symptom prior to onset of ACTH
x Indicates absence of finding initially.
* "Normal" considered any rate below 100.
** Indicates P-R interval became abnormal while on therapy.
IM - intramuscular. IV - intravenous R - remained elevated.

Many of the features of acute rheumatic fever are nonspecific and are frequently seen with any generalized infection. ACTH has its most dramatic effects on these nonspecific signs. It has been found to be an effective antipyretic in man *(18)*. Suppression of the phenomenon of local tissue reactivity and a distinct fall in gamma globulin resulting from ACTH or cortisone therapy have been noted *(5, 19, 20)*. Another interesting property of the steroid hormones is their analgesic action *(21)*. These considerations suggest that some of the favorable action of ACTH in rheumatic fever may be of this nonspecific type. The effect of ACTH on the severity and duration of carditis is equivocal. The prompt return to a normal P-R interval, heart rate, and heart size and the disappearance of pericarditis in some patients suggest that the carditis is favorably affected. On the other hand, other patients showed a persistence or recurrence of a prolonged P-R interval, significant murmurs, cardiac enlargement, and pericarditis, indicating that the progression of their carditis was not altered. The ultimate evaluation of the effects of ACTH on carditis, however, will depend on whether the patient develops permanent cardiac damage.

No rigid ACTH dosage schedule can be recommended. Although several patients responded dramatically to a certain dosage, the same dosage brought no change in others, particularly those treated intramuscularly. Only 2 patients in the series treated intravenously required an adjustment of dosage because of a persistence or recurrence of symptoms as compared with 9 of those treated intramuscularly. This discrepancy was probably the result of the hormone being destroyed at the site of injection. Each patient, therefore, must be treated on an individual basis.

A comparison of the effects of ACTH administered intravenously and intramuscularly is given in table 3. The incidence of signs of the full physiologic effect of the hormone, such as moonface and folliculitis was much higher in those treated intravenously. There was no significant difference in the general effects on carditis, weight gain, appetite, and number of recurrences following therapy in the 2 groups. The greater initial effectiveness of the drug when given intravenously was probably due to the prolonged adrenal cortical stimulation and to the elimination of the muscle "escape phenomenon." The intravenous route appears to be preferable.

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(18) Kass, E. H., and Finland, M.: Effect of ACTH on induced fever. New England J. Med. 243: 693-696, Nov. 2, 1950.

(19) Shwartzman, G.; Schaeierson, S. S.; and Soffer, L. J.: Suppression of phenomenon of local tissue reactivity by ACTH, cortisone, and sodium salicylate. Proc. Soc. Exper. Biol. & Med. 75: 175-178, Oct. 1950.

(20) Stoerk, H. C.: Inhibition of tuberculin reaction by cortisone in vaccinated guinea pigs. Federation Proc. 9: 345, 1950.

(21) Selye, H.: Anesthetic effect of steroid hormones. Proc. Soc. Exper. Biol. & Med. 46: 116-121, Jan. 1941.

IM - intramuscular.
IV - intravenous
R - remained elevated.
indicates P-R interval became abnormal while on therapy.

Undesirable side effects resulting from treatment other than moon-face, folliculitis, and abdominal adiposity were not common. The absence of electrolyte disturbance may have been due to the low sodium diet and the administration of potassium. No disturbances of carbohydrate metabolism were noted. No effect on libido was reported. Four categories of psychologic response accompanying steroid hormone administration have been described. All patients in this series experienced the sense of well-being of the grade I response as classified by Rome and Braceland *(22)*. Only 1 patient had a minor episode of disorientation which could possibly be classed as a grade IV response. It appears that ACTH even in large doses administered in conjunction with adequate control measures results in few serious complications in adults. This is in contrast to the more frequent complications reported in children.

TABLE 3. *Comparison of effects of ACTH given intravenously and intramuscularly**

How given	Fever	Polyarthritis	Sedimentation rate	P-R interval	Tachycardia
Intravenously	1.1	2.4	8.8	7.6	2.4
Intramuscularly	5.2	10.0	24.8	21.5	6.5

*Numbers indicate the average number of days required for the finding to return to normal.

Each attack of acute rheumatic fever is known to be self-limited. Withdrawal reactions as manifested by tachycardia, fever, polyarthritis, and sometimes only an elevation in the sedimentation rate were frequently observed following the completion of ACTH therapy. Similar symptoms occur following the use of salicylates in the treatment of acute rheumatic fever *(7)*. The question arises whether these withdrawal symptoms are due to the discontinuance of the medication or to a continuation or recurrence of the rheumatic process. If they indicate a recurrence or continuation of the disease, ACTH would appear to have little if any effect on the termination of the natural course of the rheumatic process. The fact that the withdrawal symptoms sometimes did not appear until from 8 to 39 days after cessation of therapy would support this contention. In all but 1 (patient 7) the withdrawal symptoms subsided spontaneously. This patient was not refractory to the hormone when a second course was given intravenously.

One death occurred in this series (patient 16) after 37 days of ACTH therapy *(23)*. Prior to death, he had a recurrence of polyarthritis, fever,

(22) Rome, H. P., and Braceland, F. J.: Use of cortisone and ACTH in certain diseases; psychiatric aspects. Proc. Staff Meet., Mayo Clin. 25: 495-497, Aug. 15, 1950.

(23) Shopfner, C. E., and Seife, M.: Rheumatic carditis and hemorrhagic pneumonitis treated with ACTH; report of fatal case. Armed Forces M. J. 3: 819-824, June 1952.

and tachycardia; he had a continuance of the carditis and a diffuse bilateral nodular pneumonitis. Postmortem examination revealed a rheumatic myocarditis and valvulitis and a hemorrhagic pneumonitis with no positive bacterial findings. This case raises the question as to the effect of ACTH on the antibody and defense functions of the body.

CASE REPORTS

Case 3. A 19-year-old man was admitted to the hospital on 7 February 1951 with his third attack of rheumatic fever. Three weeks prior to admission he had had a mild bout of pharyngitis for which he sought no medical aid. Since his last attack of rheumatic fever in 1947 he had had frequent episodes of dyspnea on exertion and mild joint pains. Just prior to admission he complained of palpitation, substernal oppression, easy fatigability, and dyspnea on exertion.

His temperature was 98.8° F. His pharynx was mildly injected. A soft systolic murmur which was accentuated by placing the patient on his left side was heard over the mitral area. There was mild pain on movement of his left shoulder. His sedimentation rate was 42. His P-R interval was 0.24 seconds.

On the fourth hospital day treatment with 20 mg. of ACTH given intramuscularly every 6 hours was started. The patient remained afebrile and his heart murmur persisted. On the seventh day of treatment the P-R interval had decreased to 0.19 seconds and the sedimentation rate was 17 mm. On the eighth day of therapy the ACTH was reduced to 15 mg. every 6 hours and, because he continued to do well, it was further reduced to 10 mg. every 6 hours on the fifteenth day of treatment. Because the P-R interval increased to 0.21 seconds on the twenty-eighth day of therapy, the ACTH was increased to 25 mg. every 6 hours. Treatment with ACTH was continued for 6 weeks. The P-R interval returned to 0.2 seconds on the fortieth day of treatment. A rise in the sedimentation rate was noted on the forty-first day of therapy. The rate did not return to normal until 23 days after the ACTH was discontinued. About 4½ months after the onset of the acute rheumatic fever, this patient was afebrile and asymptomatic. The mitral systolic murmur was still present; the ECG, sedimentation rate, leukocyte count, and teleroentgenogram were normal.

Comment. This was 1 of 2 patients in whom the P-R interval became prolonged while on ACTH therapy. (The other was patient 23.) Initially, the P-R interval returned to normal within a period of 7 days and the recurrent partial heart block returned to normal within 10 days after the dose of ACTH had been increased to 100 mg. intramuscularly every day. One must conclude that the dosage of ACTH was not adequate or that it was decreased too rapidly.

Case 7. A 20-year-old man was admitted to the hospital on 28 February 1951 because of severe pain in the knees and elbows. An upper respiratory infection and substernal tightness had also been present for 4 days. The patient's temperature on admission was 103° F. His pulse was 120. A soft systolic murmur was heard over his mitral area. His knees and elbows were painful on movement and his right knee was swollen. The leukocyte count was 16,400 with 84 percent neutrophils and the sedimentation rate was 28. The P-R interval was 0.22 seconds.

Treatment with 20 mg. of ACTH intramuscularly every 6 hours was started on the fourth hospital day. The temperature and pulse rate returned to normal in 48 hours and the joint pain subsided completely in 5 days. The P-R interval returned to normal in 7 days. The dose of ACTH was decreased to 15 mg. intramuscularly every 6 hours on the tenth day of therapy. Between the thirteenth and twenty-sixth days of treatment there was a recurrence of the polyarthritis, a rise in temperature to 101° F., an increase in the sedimentation rate to 38, and a second prolongation of the P-R interval to 0.22 seconds. The dose of ACTH was gradually increased during this period to 50 mg. every 6 hours intramuscularly. Thereafter it was gradually decreased to 100 mg. daily. Five days following the discontinuance of hormone therapy the temperature and pulse rate again became elevated, polyarthritis returned, and the sedimentation rate increased to 34. These symptoms subsided spontaneously in 5 days. The mitral systolic murmur persisted.

The patient remained well until 39 days after the ACTH had been discontinued, when the temperature and pulse rate again became elevated and the sedimentation rate rose to 37. There was pain in the left shoulder and marked substernal oppression. The heart was enlarged to percussion and the previously heard cardiac murmur persisted. Moist rales were heard at the bases of both lungs. A roentgenogram revealed a cardiac enlargement of more than 25 percent. A second course of ACTH was started, the drug being given intravenously. The patient received 25 mg. daily for the first 7 days, 20 mg. on the eighth day, 15 mg. on the ninth and tenth days, 10 mg. on the eleventh and twelfth days, and 5 mg. on the thirteenth and fourteenth days. The temperature and polyarthritis cleared within 24 hours. The substernal oppression diminished in 24 hours and cleared completely in 9 days. After the fourteenth day of ACTH therapy a cardiac enlargement of 13 percent was reported and after 19 days it was 5 percent, following which the patient remained afebrile and asymptomatic and had a normal sedimentation rate and ECG. The heart murmur persisted and the heart enlargement had returned to 15 percent 4 months after admission.

Comment. Early in this patient's first course of therapy, there was a recurrence of symptoms which required 200 mg. of ACTH a day intra-

muscularly for relief. This suggested an inadequate initial dosage. The effect of the second course of ACTH given intravenously on heart size and early congestive failure was dramatic. No specific cardiac therapy was used other than the low salt diet which alone would not account for the rapid improvement. This was the only patient whose cardiac enlargement appeared to be affected by the ACTH.

Case 15. A 22-year-old man was admitted to the hospital on 24 February 1951 complaining of pain, swelling, and tenderness in the shoulders, knees, wrists, and ankles of 24 hours' duration. About 1 week prior to admission he had had pharyngitis for which he was given 1 injection of 300,000 units of aqueous penicillin G procaine. He was acutely ill on admission. His temperature was 101° F. His pulse was 100. No heart murmurs were heard. The leukocyte count was 13,200 with 85 percent neutrophils. The sedimentation rate was 34. The P-R interval was 0.28 seconds.

Treatment with 25 mg. of ACTH every 6 hours was started on the fourth day of hospitalization. After 7 days of therapy, the temperature was 100° F., the pulse was 100, the sedimentation rate remained elevated, and the polyarthritis persisted. A mitral systolic murmur was also heard on the seventh day of therapy; the P-R interval was 0.2 seconds; and a nodal rhythm was present. The dose of ACTH was increased to 30 mg. every 6 hours intramuscularly. Within 48 hours the temperature was normal and the joint pain began to subside. The P-R interval and sedimentation rate remained elevated. The ACTH was decreased to 25 mg. every 6 hours intramuscularly on the fifteenth day of therapy. Within 48 hours the polyarthritis and fever returned. The drug was increased to 120 mg. daily, but during 8 days on this dosage the symptoms persisted. The ACTH was increased to 50 mg. every 6 hours intramuscularly on the twenty-fourth day of treatment. The abnormal temperature and pulse and polyarthritis subsided in 24 hours, completely clearing within 72 hours. The P-R interval dropped to 0.16 seconds. The dose was slowly reduced to 30 mg. every 6 hours. An aortic systolic murmur appeared on the twenty-eighth day of treatment in addition to the mitral systolic murmur. After discontinuance of therapy, a systolic murmur was heard along the left heart border. Fourteen weeks after the onset the patient was asymptomatic, but the cardiac murmurs persisted.

Comment. This case illustrates that the conventional dose of from 80 to 120 mg. of ACTH intramuscularly may be inadequate for the relief of symptoms of acute rheumatic fever. It also suggests that the progress of the carditis is not altered as evidenced by the appearance of a mitral systolic murmur and the reappearance of an increased P-R interval on the eighth and twelfth days of treatment, respectively. On the thirteenth day of treatment this patient developed a generalized urticaria which subsided in 48 hours on 100 mg. of pyribenzamine every 6 hours. The urticaria may have been due to the porcine origin of the ACTH used.

Case 23. A 21-year-old man was admitted on 31 March 1951 because of pain in the knees, wrists, elbows, and fingers of 48 hours' duration. About 3 weeks prior to admission he had had pharyngitis for which penicillin was given. His temperature was 102° F. His pulse was 100. A soft mitral systolic murmur was heard. There was marked pain on movement and tenderness, redness, and swelling of the ankles, knees, elbows, wrists, and fingers. The leukocyte count was 9,900 with 61 percent neutrophils. The hemoglobin was 12.6 grams and the sedimentation rate was 38. The roentgenogram revealed a cardiac enlargement of 8 percent. The P-R interval was 0.14 seconds.

Treatment with 25 mg. of ACTH a day intravenously was started on the third hospital day. The temperature and pulse returned to normal in 24 hours. The joint pains subsided completely in 48 hours. The heart murmur persisted. Following 1 week of ACTH therapy intravenously, 25 mg. every 6 hours intramuscularly was given for 1 week; 20 mg. intramuscularly every 6 hours for 2 weeks; 15 mg. intramuscularly every 6 hours for 1 week; and 10 mg. intramuscularly every 6 hours for 1 week. During the course of therapy the patient remained afebrile and asymptomatic. In addition to the mitral systolic murmur, an aortic systolic murmur appeared on the sixteenth day of treatment and a systolic murmur in the third left interspace appeared on the nineteenth day of treatment. These murmurs persisted to a variable degree intermittently throughout the course of therapy. The sedimentation rate became normal on the eleventh day of treatment. By the fourth day the P-R interval had increased to 0.22 seconds. It dropped to 0.2 seconds on the tenth day of therapy and remained normal until the twenty-third day of treatment at which time it again became 0.22 seconds. The patient was receiving 80 mg. of ACTH a day intramuscularly at this time. On the twenty-ninth day of therapy, the P-R interval dropped to 0.16 seconds and remained normal until 1 day after the ACTH was discontinued when it rose to 0.22 seconds. It remained elevated until 22 days after discontinuance of therapy. With an increase in the P-R interval, there was also a rise in the sedimentation rate which returned to normal when the heart block cleared. The patient became afebrile and asymptomatic 10 weeks after admission to the hospital. The heart murmurs were still present 3 months after the onset of illness.

Comment. In this patient the P-R interval became prolonged while he was receiving 25 mg. of ACTH daily intravenously and again when he was receiving 20 mg. every 6 hours intramuscularly. It also became prolonged after he had received 6 full weeks of ACTH therapy. This suggests that the ACTH had no effect on the carditis in this patient. The dose of ACTH was not increased when the P-R intervals became prolonged and, therefore, one might consider that the dose was inadequate at that time. The P-R intervals did, however, return to normal without an increase in dosage. If the dose had been increased, the return of the P-R interval to normal probably would have been

falsely attributed to this increase. Thus, one can readily see why any drug used in the treatment of acute rheumatic fever is difficult to evaluate.

CONCLUSIONS

ACTH in adequate doses has a marked beneficial effect on the signs and symptoms of acute rheumatic fever (excluding carditis). The response to intravenous administration is much more dramatic than that to intramuscular administration. The effect of the hormone on the severity and duration of rheumatic carditis is equivocal regardless of the route of administration. Serious complications resulting from therapy were not encountered in our series of 30 patients. Signs of full physiologic effect such as moonface, folliculitis, strias, and abdominal adiposity were common, occurring more frequently in the patients treated intravenously. The most useful and practical guide to the adequacy of therapy is the clinical response of the patient. The dosage schedule must be adjusted to fit the individual patient. The withdrawal symptoms cleared spontaneously in all but 1 patient.

BOOK REVIEWS

Mental Disorders, Diagnostic and Statistical Manual, prepared by the *Committee on Nomenclature and Statistics of the American Psychiatric Association.* 130 pages; illustrated. American Psychiatric Association, Mental Hospital Service, Washington 6, D. C., publisher, 1952. Price $1.50.

There has been a great need to bring our system of psychiatric nomenclature into line with the true status of our scientific progress in the understanding of mental disorders. This has been done only in this book. This monograph offers a completely new classification in conformity with newer scientific and clinical knowledge, though the statement that it is "simpler in structure" or "easier to use" is open to question because it describes no less than 9 types of schizophrenic reactions. Nonetheless, the new nomenclature does allow more freedom, flexibility, and exactness in classifying the many and varied types of reactions seen in psychiatric practice and it has been incorporated in the 1952 edition of "Standard Nomenclature of Diseases and Operations."

Essentially this is a reference manual which will be widely used not only by psychiatrists but also by medical record custodians because it correlates and cross-indexes this new nomenclature with the international classification. It should obviate some of the confusion that has heretofore existed.

The Committee compiling this manual recognized the disadvantages of using descriptive terms and deplored the incomplete state of psychiatric knowledge that forces us to use terms and definitions that are as yet not unanimously agreed on. Because so many psychiatrists, among them Janet and Cobb, have commented on the impossibility of defining satisfactorily the terms "psychosis" and "neurosis," one wonders why the false dichotomy implied therein must be perpetuated. There are other definitions, for example, of the terms "psychoneurotic reaction" on page 13, which would include everyone who uses certain defense mechanisms to mitigate their anxieties, but imperfections of this sort will undoubtedly be eliminated in future editions and definitions will be classified and refined so as to be more exact and exclusive. In present-day clinical psychiatry, the trend is away from mere labeling, necessary as this may be for statistical purposes, because diagnosis in terms of dynamic formulations that more fully portray the clinical findings is more meaningful. Provision for this is made in this monograph in Section III which deals with the necessity for a complementary diagnostic evaluation in terms of the external stress, the premorbid personality and predisposition, and the degrees of psychiatric impairment.

The Committee is to be commended for completing a herculean task. As this manual achieves its deserved widespread use, it will provide a stimulating challenge to psychiatrists to correlate their clinical thinking and their nosologic classifications.

—*Capt. J. F. McMullin, MC, U. S. N.*

Mind, Perception and Science, by *W. Russell Brain,* D. M., F. R. C. P., President of the Royal College of Physicians of London. 90 pages. Charles C Thomas, Publisher, Springfield, Ill., 1951. Price $2.50.

This book consists largely of lectures and broadcasts of a philosophic nature dealing primarily with hypothetical relationships between cerebration and such behavioral phenomena as perception, linguistics, consciousness, imagery, memory, and feeling. It is well written, entertaining, and for the most part intelligible to an educated layman. The general flavor is that of an earnest, sophisticated after-dinner conversation among "intellectuals," in which there is much dealing in generalities, frequent deviation from the central theme, and the occasional emergence of sparkling oddities of thought. The book lacks the unity, persuasiveness, and orderliness of argument characteristic of the scientific treatise. It is also short on experimental documentation, which, as almost everyone who reads it will understand, represents the author's choice rather than his limitation.

—*Maj. R. B. Payne, U. S. A. F. (MSC)*

Odontoma and Impacted Left Mandibular Cuspid

William D. Bumsted, *Major, DC, U. S. A. (1)*

ODONTOMAS are benign tumors which arise from one or many of the components of the tooth germ. They may occur in either the mandible or the maxilla. Many of these tumors appear to be abortive attempts at tooth development. These lesions may develop from either ectodermal or mesodermal elements of the tooth germ or from both. The age at which they develop determines the form they may take. If they arise early in the development of the tooth germ, no dental structures are evident. These are soft odontomas. If they arise late in the development of the tooth germ, they may be composed of dentin, enamel, or cementum, or a combination of these structures. These are hard or calcified odontogenic tumors. Odontomas are clinically significant because of their destructive capacity and their inhibiting influence on the eruption of the teeth.

CASE REPORT

A 27-year-old Negro reported to the dental clinic on 16 January 1952. He stated that he had had bad teeth since childhood and had lost several teeth through infection, trauma, and neglect. He had had a retained deciduous tooth in the mandibular left cuspid region until he was 14 years old. This tooth then became loose and was lost. This area never caused the patient any discomfort and he was unaware that he had an impacted permanent tooth and an odontoma beneath the gingival tissue until they were observed in our routine roentgenograms.

On examination he was found to have 8 maxillary and 5 mandibular teeth missing. Seven maxillary and 8 mandibular teeth were carious. Although his mouth revealed evidence of poor oral hygiene, the gingival tissues appeared to be in good condition. There was no lymphadenopathy of the submaxillary, sublingual, or superficial cervical lymph nodes.

Roentgenograms confirmed the clinical findings and revealed a radiopaque mass the size of a pea in the mandibular process about 5

(1) Camp Stoneman, Pittsburg, Calif.

mm. beneath the alveolar crest between the left lateral and the left first bicuspid (figs. 1-3). This mass with its circumscribed area of radiolucency had the appearance of an odontoma. About 3 mm. beneath this mass, the crown of an impacted mandibular cuspid was visible. There was evidence of osseous destruction surrounding the crown of the impacted tooth, which gave the impression of a follicular cyst. The long axis of the tooth was in the distal angular position. The apex of the root was about 5 mm. from the inferior border of the mandible. The crown of this impacted tooth appeared to be impinging on the root of the left mandibular first bicuspid. A tentative diagnosis of

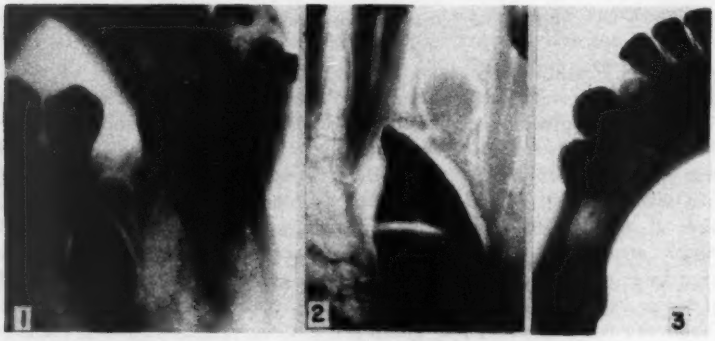

Figure 1. Lateral roentgenogram of the left mandible revealing an odontoma and an impacted cuspid. Figure 2. Roentgenogram of the crown of the impacted cuspid and a follicular cyst. The odontoma is circumscribed by a fibrous radiolucent capsule. Figure 3. Occlusal roentgenogram of the left mandible showing the odontoma and impacted cuspid lying between the lateral incisor and the first bicuspid.

calcified odontoma and an impacted left mandibular cuspid with a follicular cyst was made.

In view of the findings, it was planned to remove the impacted cuspid, the follicular cyst, and the odontoma. Because most of the remaining teeth in the mandible were restorable, it was planned to restore them and construct a lower partial denture. On 29 January, under block anesthesia, a semilunar incision was made from the mandibular left central incisor to the left second bicuspid and the mucoperiosteal flap was retracted. The bone overlying the odontoma and the crown of the impacted cuspid was carefully removed. The odontoma was found to be encapsulated in a tough fibrous sac. The tumor and the sac were completely removed.

In removing the impacted cuspid care was taken (1) to conserve the surrounding bone; (2) to preserve the left mandibular first bicuspid which was in a precarious position because of the impingement of the crown of the impacted cuspid on its apex; and (3) because of the proximity of the inferior dental canal to the impacted cuspid, to prevent

damage to the inferior alveolar nerve. The crown of the impacted cuspid was amputated with a fissure bur and lifted out with the follicular cyst. Because of the position of the long axis of the tooth there was insufficient space to remove its root. Rather than destroy any more bone by exposing more of the root, a small notch was cut in the visible portion of the root, an elevator was inserted, and the root was raised as far as possible. This portion of the root was then sectioned with a bur and removed, which left adequate space for the remaining portion of the root to be removed, thus conserving the bone and minimizing trauma.

All bone fragments and debris were thoroughly removed and the entire area was inspected for any remnants of the follicular sac or granulation tissue. The mucoperiosteal flap was sutured in place.

The patient made an uneventful recovery. Microscopic sections of the decalcified specimen revealed an encapsulated lesion, the central portion of which was occupied by enamel showing a disordered prismatic pattern. Irregular eosinophilic formations with the fibrillar structure of dentin were seen about the periphery. Basophilic calcified structures which might represent cementum were seen in close association with these. Moderate numbers of associated, small, dark, elongated cells, which were presumably odontoblasts and cementoblasts, were also seen. No ameloblasts were observed in association with enamel. The provisional diagnosis of calcified odontoma with a follicular cyst about the crown of the impacted left mandibular cuspid was thus confirmed.

BOOK REVIEWS

The Fight Against Tuberculosis, An Autobiography, by *Francis Marion Pottenger,* M. D. 276 pages; illustrated. Henry Schuman, New York, N. Y., publisher, 1952. Price $4.

This book is a double feature in that it includes a well-written autobiography and an eye-witness account of the modern conquest of tuberculosis from the discovery of the causative organism by Koch up to, but not including, the advent of the isonicotinic acid hydrazides of today. The author tells the story of (1) his childhood and adolescence on an Ohio farm; (2) the inspiration furnished him to become a physician by the family doctor; (3) the financial struggles, disappointments, and frustrations of his years in medical school; and (4) the early phases of his life as a private practitioner. In addition to the usual handicaps,

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he had to develop extreme powers of concentration because his reading abilities were limited by poor eyesight.

The first Mrs. Pottenger acquired pulmonary tuberculosis, and it was this that changed Dr. Pottenger's plans for a career in surgery in nearby Cincinnati to that of a phthisiologist in Monrovia, Calif. His descriptions of the old masters of Vienna, their clinics, discoveries, greatness, feuds, errors, and frailties are entertaining and convincing. He reveals the fineness and greatness of his own character, his zeal, ambitions, and accomplishments, but also uncovers his own stubbornness in ascribing undue therapeutic value to tuberculin and in the maintenance of the accuracy of outlining visceral organs by light palpation.

Dr. Pottenger is among those who deserve much credit for the reduction in the death rate from tuberculosis, from 201 per 100,000 in 1900 to 22.2 in 1951. This was achieved without the use of any chemical specific and was due to education, a hygienic regimen, and the personal devotion of such great masters as Dr. Pottenger. Moreover, he pioneered in the establishment of the American College of Physicians, the Society for the Study of Internal Secretions, and the study of allergy. He was always a leader in civic and political affairs.

This book is a "must" for all students of tuberculosis and should be read by all internists, those interested in public health, and those who are struggling to eradicate such chronic diseases as cancer, heart disease, multiple sclerosis, and rheumatoid arthritis. This book is recommended highly to lay readers as a fascinating story of a great man's life in the conquest of tuberculosis.—*Capt. J. Love, MC, U. S. N.*

Military Medical Manual, March 1952. 7th edition. 761 pages; illustrated. The Military Service Publishing Company, Harrisburg, Pa., publisher, 1952.

This book with a foreward by Major General George E. Armstrong, The Surgeon General, U. S. Army gives comprehensive, concise, authentic, up-to-date information on medicomilitary service. It is a remarkably readable book that is well illustrated, making the subject matter most interesting and instructive.

Part I is devoted to the (1) organization, functions, and tactical employment of the various arms; (2) command-staff procedures; (3) leadership; (4) map reading; and (5) customs and courtesies of the service.

Part II deals with (1) the organization and functions of the Army Medical Service; (2) preventive medicine; and (3) medical aspects of atomic, biologic and chemical warfare.

Part III covers (1) supply; (2) the training of individuals and units; and (3) the Medical Service in a theater of operation. This arrangement makes the subject matter readily available for study and reference and, therefore, a worth-while addition to the library shelf of every Medical Service officer.—*Col. P. I. McSbane, MC, U. S. A.*

Reflux Blood in the Gallbladder[1]

David D. Greene, *Captain, MC, U. S. N.*
Luis Marroquin, *Lieutenant, MC, U. S. N. R.*
Sellers J. Thomas, Jr., *Lieutenant, MC, U. S. N. R.*

HEMOCHOLECYST or blood-filled gallbladder is an extremely rare condition which none of us had encountered previous to observing the case to be described. In a review of the textbooks and recent literature, no case similar to ours was found. This condition has been attributed to: (1) acute hemorrhagic cholecystitis (2); (2) cholelithiasis with erosion (2); (3) neoplasm, benign or malignant, with ulceration (3); and (4) other conditions such as hypertension, hemorrhagic diathesis, aneurysm, and infarct of the gallbladder and biliary system (4-6). Aschoff (5) is cited as having stated that hemorrhages and ecchymoses of the gallbladder may occur in patients with hemorrhagic diathesis.

It is conceivable that this condition could result from a reflux in the presence of an upper gastrointestinal hemorrhage due to an internal biliary fistula (7) or an incompetent sphincter of Oddi. It has been shown that air or barium sulfate from a gastrointestinal series can pass into the biliary system from the gastrointestinal tract via an internal

(1) U. S. Naval Hospital, Corpus Christi, Tex.

(2) Walters, W., and Snell, A. M.: Diseases of the Gallbladder and Bile Ducts. W. B. Saunders Co., Philadelphia, Pa., 1940. pp. 128-129.

(3) Walters, W.; Snell, A. M.; Judd, E. S., Jr.; and Butt, H. R.: Surgery of the biliary system. In Walters, W. (editor): Lewis' Practice of Surgery. W. F. Prior Co., Inc., Hagerstown, Md., 1949. vol. 7, chap. 2.

(4) Christopher, F., and Salvage, J. L.: Apoplexy of gallbladder. Surgery 24: 864-866, Nov. 1948.

(5) Aschoff, L.: Cited in Uriburu, J. V., Jr.: Apoplejía de vesícula biliar; infarto de vesícula biliar. Rev. Asoc. méd. argent. 60: 508-516, June 30, 1946.

(6) Case 33241. (Periarteritis nodosa involving gallbladder and liver; infarcts of gallbladder.) Case Records of the Massachusetts General Hospital. New England J. Med. 236: 909-913, June 12, 1947.

(7) Bockus, H. L., et al.: Gastro-Enterology; Volume III: Diagnosis and Treatment of Disorders of the Liver, Gallbladder, Biliary Tract and Pancreas. W. B. Saunders Co., Philadelphia, Pa., 1946. p. 707.

biliary fistula *(8)*. Sullivan and Hamman *(8)* stated that "an atonic sphincter of Oddi is so rare that it need not be considered as permitting air or barium sulfate to get into the biliary system." Incompetence of the sphincter can be due to local destruction, scarring, or traction, the cause being (1) a duodenocolic fistula *(9)*, (2) the passage of a stone *(10)* or an adjacent malignancy *(10)*, or (3) the prolonged use of a drainage tube through the ampulla of Vater with resulting fibrosis of the sphincter *(11)*.

CASE REPORT

First admission. A 47-year-old man, who had been retired in 1947 because of asymptomatic hypertension, was admitted to the hospital on 14 November 1951 complaining of intermittent epigastric pain of 6 weeks' duration. Without previous episodes, while standing talking to a friend on 6 October, he suddenly had a severe cramping pain in the epigastrium with radiation along the left costal margin. This pain lasted about 45 minutes and was followed by complete relief after a sedative was administered by his physician. During the 6 weeks prior to admission, the patient had several similar attacks of less severity. No nausea or vomiting was present during the attacks and there was no relation to food intake. On two occasions during this period, he noticed black stools. There was no recent weight loss.

On admission his blood pressure was 190/120. His skin was sallow and there was a questionable icteric tinge of the sceleras and palate. His erythrocyte count was 3,680,000; hemoglobin, 11 grams. His sedimentation rate was 25. His urine was normal except for the presence of a few leukocytes. His nonprotein nitrogen was 40 mg. per 100 cc. His cephalin-cholesterol flocculation was 1 plus in 24 hours and 2 plus in 48 hours. His fasting blood glucose was 166 mg. per 100 cc. His glucose tolerance test showed a mild diabetic tendency, but no specific therapy was indicated. His ECG showed suggestive evidence of left ventricular hypertrophy. No change was noted on subsequent ECG's. Visualization of his upper gastrointestinal tract revealed a small hiatus hernia.

He had repeated episodes of epigastric pain of increasing severity and required narcotics for relief. Physical examinations at these times were negative except for epigastric tenderness and voluntary spasm over the upper abdomen. No residual subjective or objective findings were present in the interim.

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(8) Sullivan, J. M., and Hamman, L.: Internal biliary fistula due to peptic ulcer. Arch. Surg. 63: 635-640, Nov. 1951.

(9) Rees, C. E.: Duodenocolic fistula with incompetent sphincter of Oddi. J. A. M. A. 100: 496-497, Feb. 18, 1933.

(10) Puestow, C. B.: Spontaneous internal biliary fistula. Ann. Surg. 115: 1043-1054, June 1942.

(11) Bockus, H. L., et al.: Gastro-Enterology; Volume II: The Small and Large Intestine and Peritoneum. W. B. Saunders Co., Philadelphia, Pa., 1944. p. 97.

On 1 December he passed grossly bloody stools associated with pain in the epigastrium and left upper abdominal quadrant. His hematocrit was found to be 24 and his hemoglobin was 8.5 grams. A whole blood transfusion of 500 cc. was given. Melena persisted and on the following day the hematocrit was 23. A liter of whole blood was administered and on 3 December the hematocrit was 28. Another 500 cc. of blood was given that day, and the hematocrit rose to 31 on 4 December. Tarry stools continued without nausea or vomiting. A Levin tube passed into the stomach produced no blood. The condition was complicated by a pyrogenic transfusion reaction with a temperature of 105° F., but this subsided rapidly. On 6 December the status had improved somewhat although melena persisted and an emergency exploratory laparotomy was scheduled. A blood transfusion was started and he was sent to surgery.

A right paramedian incision was made. The small bowel was somewhat distended, containing a large amount of liquid and clotted blood. The duodenum appeared somewhat enlarged and contained a great amount of dark clot, as was demonstrated later at the resection. The stomach was empty except for the Levin tube. There was much fibrosis about the pyloric ring and an indurated perforating ulcer with a crater about 1.5 cm. in diameter could be felt on the posterior wall of the first part of the duodenum. The pancreatic head felt slightly enlarged and firm, the body and tail being normal. The gallbladder was distended, but not thick-walled, and the contents appeared through the wall to be blue-black. The liver and common duct felt normal. In the hepatoduodenal ligament a lymph node measuring about 1 by 2 cm. was noted. On frozen section this showed chronic, nonspecific lymphadenitis.

Palpation through the foramen of Winslow revealed no evidence of induration, stone, or fistula between the duodenum and the biliary system. A partial gastrectomy was performed. The duodenum was dissected off the head of the pancreas with great difficulty and moderate bleeding. A clamp was placed across the duodenum distal to the ulcer, and it was transected. In attempting to invert the duodenal stump, the friable posterior wall tore away from the clamp. The clamp was removed and a continuous running stitch was started on the anterior duodenal wall and continued posteriorly, gradually pulling up the posterior wall to effect a closure. The anterior wall was then pulled over, sutured to the pancreas, and covered with adjacent mesentery. Only half of the stomach was then resected. The lesser curvature was infolded, because of the technical difficulties with hemorrhage, and an antecolic isoperistaltic end-to-side gastrojejunostomy was performed.

Prior to closure of the anastomosis the Levin tube was passed into the proximal limb past the ligament of Treitz. An incision was made in the fundus of the distended gallbladder and about 20 cc. of dark clot and 15 cc. of bile-stained blood issued forth. The organ was inspected

and spooned out and no stone, debris, or tissue was produced. A mushroom catheter was introduced into the fundus and secured with a purse-string suture and brought out through a lateral stab wound. The abdomen was closed with doubled through-and-through No. 32 stainless steel wire sutures. The patient received 1,000 cc. of whole blood during the operation and was returned to the ward in satisfactory condition with suction to the Levin tube.

Postoperatively the blood pressure rose to 225/134 and gradually returned within a week to 155/100. Blood-stained bile drained from the gallbladder for 24 hours, following which the bile became clear. Later it became thick and dark, having the appearance of concentrated bile. The amount drained in the first 48 hours was 950 cc. from the gallbladder and only 180 cc. from the Levin tube in spite of frequent irrigations with 5 cc. of normal saline solution to insure the patency of the tube. Until the fifth day, when the Levin tube was removed, this disparity in drainage continued. This led one of us (DDG) to question whether an elective cholecystostomy would be of value in relieving intraduodenal tension. It was thought that this might eliminate the need for a duodenostomy *(12)* if only an insecure closure of the duodenal stump could be obtained. The patient passed daily liquid black stools from the third until the ninth postoperative day when the stools became normal.

He was given transfusions of 500 cc. of blood on the first and third postoperative days. On the third day he developed a right-sided pulmonary atelectasis which cleared with intratracheal aspiration. Abdominal distension was a disturbing symptom in the first postoperative days but it subsided promptly. There was no evidence of further bleeding and on the fourth postoperative day the hematocrit was 37. Fluid and electrolyte balance were maintained and the patient showed progressive clinical improvement daily. On the tenth postoperative day cholangiography, through the gallbladder tube, demonstrated well-filled hepatic and common ducts (fig. 1). No evidence of calculi or debris was present. A few small negative shadows were noted within the common bile duct, but these were definitely air bubbles introduced at the time of the study. The gallbladder did not fill because the common bile duct emptied rapidly. The gallbladder tube was removed on the fourteenth postoperative day and the sinus stopped draining 3 days later. An oral cholecystogram on the twenty-ninth postoperative day revealed that the gallbladder failed to concentrate the dye. On the same day visualization of the upper gastrointestinal tract revealed a normally functioning stoma at the site of the gastroenterostomy with no evidence of a marginal ulcer. The previously described diaphragmatic hernia persisted.

(12) Priestly, J. T., and Butler, D. B.: Duodenostomy; method of managing duodenal stump in certain cases of partial gastrectomy. Proc. Staff Meet., Mayo Clin. 26: No. 4: 65-69, Feb. 14, 1951.

Forty-four days after operation (19 January 1952) the patient was discharged. He was asymptomatic and was eating small but frequent meals. There had been no recurrence of the preoperative pain or bleeding. His hematocrit was 40, with a hemoglobin of 13 grams.

Figure 1. Postoperative cholangiogram revealing a shrunken gallbladder with a normal biliary tree.

Second admission. On 1 February, 13 days after discharge, the patient was readmitted to this hospital complaining of a moderately severe epigastric pain of 2 days' duration relieved by drinking milk. Mild episodes of a similar type recurred throughout the day and a tarry stool was passed. On the day of admission the patient was awakened at 0400 by a similar episode and vomited about a cupful of coffee-ground material. In the next week at intervals he had re-

current episodes increasing in frequency and severity and productive of grossly bloody vomitus. His abdomen, except at the time of seizures, was perfectly soft without tenderness or mass, but during a paroxysm, which started in the epigastrium and radiated along the left costal margin, marked rigidity of the upper part of his abdomen was present. Transfusions were given and the hemoglobin increased.

His blood pressure was unstable, ranging from 168/100 to 100/70, rising following transfusion to 150/94. A gastrointestinal series revealed no definite ulcerated lesion. The stomach emptied satisfactorily. Oral cholecystography on 5 February demonstrated a nonfunctioning gallbladder.

He was taken to surgery on 11 February with a preoperative diagnosis of marginal ulcer with impending perforation. At operation massive adhesions were found between a thickened, indurated gallbladder, the transverse colon, and the anastomosis. An intragastric mass could be felt along the lesser curvature in juxtaposition to the anastomotic site. Resection of all but one-third of the remaining stomach, including the entire lesser curvature, was performed. Following this, the thick-walled gallbladder was removed from above downward. Blood was administered during and following the operation and the patient's condition stabilized satisfactorily. Examination of the removed stomach revealed no marginal ulcer but a polypoid mass with a longitudinal broad pedicle measuring about 5 by 3 cm. It was our impression that this could have resulted from the infolding of the lesser curvature at the previous operation.

Gross and microscopic examination of the gastric specimen revealed evidence of satisfactory healing at the old anastomosis, although there was a small abscess in the stomach wall near the suture line. Chronic gastritis was present, but no bleeding sites were noted. The previously described polypoid mass proved to be due to a localized area of submucosal edema. The gallbladder showed chronic and acute cholecystitis.

A lower nephron nephrosis developed and a rapidly downhill course ensued with evidence of a generalized peritonitis the third postoperative day. The patient died on the fourth postoperative day.

Autopsy revealed a generalized purulent peritonitis and a left subphrenic abscess. Gross and microscopic studies of the gastrojejunostomy revealed necrosis along the anastomosis and microscopic abscesses in the stomach wall close to the suture line. The liver showed mild cirrhosis with focal necrosis and the spleen, toxic splenitis. The common bile duct and hepatic ducts were patent and there was no evidence of leakage or of fistula. The ampulla of Vater was slightly larger than normal and edematous. It very readily admitted a probe. The kidneys presented the findings of arteriolar nephrosclerosis with superimposed lower nephron nephrosis. Partial atelectasis of the right

lung and an acute diaphragmatic pleuritis on the left were noted. No esophageal varices or other evidence of portal hypertension were demonstrated. Microscopic investigation failed to reveal any evidence of periarteritis nodosa and/or infarction.

COMMENT

We believe that this patient at the time of the first operation had had a subacute perforation of a posterior duodenal ulcer which had been present for some time. This produced scarring which in turn produced traction at the valve of Oddi rendering it incompetent. This for some reason did not become evident in the preoperative barium studies. This conclusion has been reached by exclusion of the other possible causes for hemocholecyst.

It is speculated that the recurrence of hemorrhage and pain was the result of the presence of the above-mentioned intragastric polypoid mass which became eroded and produced pain by impinging on and obstructing the gastrojejunal stoma. This complication would not occur in the usual partial (3/4 to 4/5) gastrectomy in which the lesser curvature had been excised. The cause of death (peritonitis) was due to necrosis and leakage of the suture line at the anastomosis performed in the presence of local infection about the gallbladder and in the remaining stomach wall. The pathologic findings in the kidneys, liver, and spleen may be attributed to the overwhelming infection.

SUMMARY

Hemocholecyst developed presumably as the result of reflux from the duodenum in a patient with massive hemorrhage from a duodenal ulcer. Although cholecystotomy relieves intraduodenal tension in the presence of an insecure duodenal stump, duodenostomy is preferable because in the presence of localized infection remaining from a previous perforation of a duodenal ulcer, drainage of a normal gallbladder results in a nonfunctioning gallbladder as demonstrated here and in one otherwise successful subsequent case *(13)*. It is in just such patients with infection that the need for decreasing intraduodenal tension arises. Furthermore, duodenostomy complicates the convalescent period very little except for care in protecting the skin and the need for additional fluid and electrolytes.

(13) Three months after operation this patient was entirely asymptomatic and an oral cholecystogram revealed a normally functioning gallbladder.

BOOK REVIEW

Clinical Dental Roentgenology, Technic and Interpretation, including roentgen studies of the child and the adolescent, by *John Oppie McCall,* D. D. S., F. A. C. D., Former Director, The Murry and Leonie Guggenheim Dental Clinic; Former Professor of Periodontia, New York University College of Dentistry; Consultant to the Dental Service, New York Hospital; Associate in Public Health and Preventive Medicine, Cornell University College of Medicine; Oral Diagnostician, New York Eye and Ear Infirmary; Diplomate, American Board of Periodontology; former Lieutenant Commander, Dental Corps, United States Naval Reserve; and *Samuel Stanley Wald,* D. D. S., F. A. C. D., Clinical Professor of Oral Cancer and Roentgenology, New York University College of Dentistry; Lecturer in Dental Roentgenology and Oral Diagnosis, New York University College of Medicine and Bellevue Medical Center and Postgraduate Medical School; Former Head of the Department of Diagnosis and Roentgenology, The Murry and Leonie Guggenheim Dental Clinic and School for Dental Hygienists; Special Lecturer in Roentgenology and Oral Diagnosis, U. S. Naval Dental School, National Naval Medical Center, Bethesda, Md.; Consultant in Charge of Roentgenology and Oral Diagnosis, U. S. Naval Hospital, St. Albans, N. Y.; Consultant in Charge of Roentgenology and Oral Diagnosis, Dental Clinics of the Community Service Society of New York; Diplomate in Oral Surgery, New York State Board of Oral Surgery; Captain, Dental Corps, United States Naval Reserve. 3d edition. 384 pages; 1,277 illustrations on 475 figures. W. B. Saunders Co., Philadelphia, Pa., publisher, 1952.

The third edition of this text presents several new features in addition to a comprehensive coverage of roentgenologic technic. The text and excellent illustrations of such abnormal conditions as cysts, bone dysplasias, and benign and malignant tumors, not commonly encountered in routine dental practice, should provide a valuable reference text for every dentist who may encounter the unusual. A thorough discussion is presented on differential diagnosis between normal landmarks and pathologic indications. The interpretation of all types of intraoral and extraoral roentgenograms is fully discussed and adequately illustrated. A field, not often included in dental texts, is presented in a brief but adequate discussion of electricity and roentgenology, safety factors, and a method of computation of x-ray radiation. All the accepted newer technics, including the long cone technic and cephalometry, are carefully described and well illustrated. Appropriate emphasis is placed on proper exposure and processing in order to secure roentgenograms which permit careful interpretation. The technic described in this text, if followed, should assure that result. This feature will be of interest to dental students and dental roentgenographic technicians as well as to experienced dentists who must ultimately be able to recognize good roentgenograms before attempting an interpretation. It was gratifying to discover that, in contrast to many other texts, no effort was made to present technics for nondental roentgenography of arms, chests, and other areas for which dental equipment is not designed.

—*Capt. K. O. Turner, DC, U. S. N.*

Diphtheria Simulating Peritonsillar Abscess and Complicated by Myocarditis[1]

Frederic S. Glazener, *Major, MC, U. S. A.*
Aubrey K. Brown, *Lieutenant Colonel, MC, U. S. A.*
Thomas W. Mattingly, *Colonel, MC, U. S. A.*

DIPHTHERIA was one of the communicable epidemic diseases the clinical manifestations of which were described by Aretaeus in the second century. According to medical historians, it was the malady which killed George Washington. The modern recognition of diphtheria, however, dates from the study of Bretonneau in 1826. The purpose of this article is to emphasize (1) that clinical findings similar to those of peritonsillar abscess are seen in a significant number of early cases of diphtheria and (2) that T-wave and RS-T segment changes are the most common electrocardiographic abnormalities observed in diphtheritic myocarditis. Two cases of diphtheria are reported, both simulating peritonsillar abscesses and both developing myocarditis, one with a fatal termination.

Diphtheria was one of the most important infectious diseases of World War II, occurring in both civil and military populations in Europe and Japan. In 1943, an estimated 1,000,000 cases occurred among civilians on the European continent (excluding the U. S. S. R.) with a case fatality rate which approximated 5 percent (2). Diphtheria was not a serious problem among the United States Forces in Europe during combat, but following the surrender of Germany in May 1945 and the closer contact of troops with the civil population during occupation, the disease reached epidemic proportions (6 cases per thousand per year) during the first 6 months of 1946. This outbreak is explained by the fact that about 30 percent of the troops under 35 years of age were Schick-positive or combined reactors and that the incidence of

(1) Walter Reed Army Hospital, Washington, D. C.
(2) Stock, A. H.: Observations on diphtheria and diphtheria bacilli in 5th Army troops in Italian campaign. Mil. Surgeon 103: 121-125, Aug. 1948.

diphtheria in the German civil population at that time was about 2.6 cases per thousand per year (3).

Many important observations were made from the study of patients with diphtheria in the European Theater of Operations. Cutaneous infections and postdiphtheritic polyneuritis with features of the Guillain-Barré syndrome were encountered. Many had atypical membranes resembling those of follicular tonsillitis. Marked faucial edema was often present with no membrane, or with a follicular or confluent exudate which could be readily wiped away with a swab (2).

In Edwards' analysis of 100 patients who died of diphtheria occurring in U. S. Army hospitals from 1943 to 1947, only 18 were correctly diagnosed on admission (4). Diphtheria was frequently diagnosed as peritonsillar abscesses. In the above-mentioned series of 100 patients, 25 were diagnosed as having peritonsillar abscess on admission and, because of this original erroneous impression, incision and drainage of the tonsils was performed on 13.

Six hundred patients with diphtheria were studied at the 97th General Hospital in the 15-month period from September 1945 to December 1946 (5, 6). An ECG was taken as soon as diphtheria was suspected clinically, or when a positive culture was reported, and the tracings were repeated at weekly intervals or oftener if indicated. Of these 600 patients, 143 (23.9 percent) showed electrocardiographic changes at some time during hospitalization; 128 of these showed abnormalities involving the T waves and RS-T segments. These abnormalities consisted of low voltage or negative T waves and depressed RS-T segments. Two patients, both of whom had negative T waves in all leads, died. Prolongation of the P-R interval above 0.22 second occurred in 11 patients. These studies did not confirm the commonly held opinion that prolongation of the P-R interval is the most common electrocardiographic abnormality observed in diphtheritic infections. Slight prolongation of the QRS complex with slurring and splintering of these complexes were common, although significant prolongation was present in only 2 patients, both of whom had a definite right bundle-branch block.

CASE REPORTS

Case 1. A 29-year-old man noted pain and swelling in the right side of his throat on 1 December 1934 while at home on pass. On the following day, because of difficulty in swallowing and breathing, he con-

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(4) Edwards, W. M.: Analysis of fatal cases of diphtheria. U. S. Armed Forces M. J. 2: 217-227, Feb. 1951.

(5) Altshuler, S. S., and Fitzgerald, P. J.: Heart in diphtheria. M. Bull., Chief Surgeon, European Command (No. 1) 4: 3-6, Sept. 1947.

(6) Altshuler, S. S.; Hoffman, K. M.; and Fitzgerald, P. J.: Electrocardiographic changes in diphtheria. Ann. Int. Med. 29: 294-305, Aug. 1948.

sulted his family physician who painted his throat. He was not improved on the third day and the family physician incised what he believed was a peritonsillar abscess, but little relief was obtained. The patient returned to camp that same evening and was admitted to the contagious disease ward of this hospital the next morning, 4 days after the onset of symptoms.

On admission, he appeared acutely ill. His temperature was 99° F. His pulse was 100. His respirations were 20. His blood pressure was 130/80. He talked with difficulty as his mouth could be opened only slightly. The posterior pharyngeal wall could not be seen because of a massive swelling in the right tonsillar region. A thick, grayish yellow, necrotic membrane covered the anterior part of the swelling and extended on to the soft palate. The membrane was removed with difficulty, leaving a bleeding surface. The anterior cervical nodes were enlarged on the right side and associated with marked induration of the soft tissues in the neck.

His leukocyte count was 16,500 with 85 percent neutrophils. His platelet count was 54,310 and the clot retraction was but slight after 18 hours. One to two plus albumin was present in his urine. Cultures of his throat and from the removed membrane were positive for *Corynebacterium diphtheriae*. An ECG taken on 11 December, showed auriculoventricular block, right bundle-branch block, low voltage T waves in lead I, and RS-T segment depression in leads II and III (fig. 1).

In the first 24 hours, 40,000 units of diphtheria antitoxin were given intravenously and 30,000 units were given intramuscularly. An additional 30,000 units were given on the sixth day. Direct transfusions of whole blood were given on the third and seventh days, following which his platelet count reached 314,000. His throat improved after the second hospital day, but difficulty in swallowing persisted with regurgitation of fluid through his nose. The adenitis and cellulitis subsided with the local application of heat, but marked weakness and prostration continued in spite of the local improvement. A few transient extrasystoles were noted on the third day and on the seventh day his pulse became grossly irregular with dropped beats, followed by a drop in blood pressure to 90/80, with circulatory collapse, frequent vomiting, and progressive cyanosis. The patient died 12 days after the onset of the disease and 8 days after hospital admission.

At autopsy the heart weighed 410 grams, was dilated, and the muscle wall of the entire left ventricle, including the interventricular septum, was brown-gray. Throughout the myocardium there were large areas showing pale yellow mottling. Below the anterior cusp of the aortic valve, there was an area of subendocardial hemorrhage. The lumen of the left atrial appendage was filled with a large, firm fibrinous clot. Microscopic study of the myocardium revealed advanced necrosis. The muscle fibers were hyalinized and broken into large and shapeless fragments. The cellular infiltration varied in different

areas. The smaller and more recent areas of necrosis showed a preponderance of neutrophils with an occasional eosinophil. In the larger and older areas, there was a more massive infiltration with lymphocytes, plasma cells, and large monocytes. The fragments of necrotic muscle, for the most part, were autolyzed. Some fibers of the papillary muscles had hydropic cell bodies and were without nuclei. An anatomic and microscopic diagnosis of (1) acute parenchymatous degeneration of the myocardium (toxic, diphtheritic); (2) acute reparative inflammatory reaction (diphtheritic myocarditis); (3) acute dilatation of the heart;

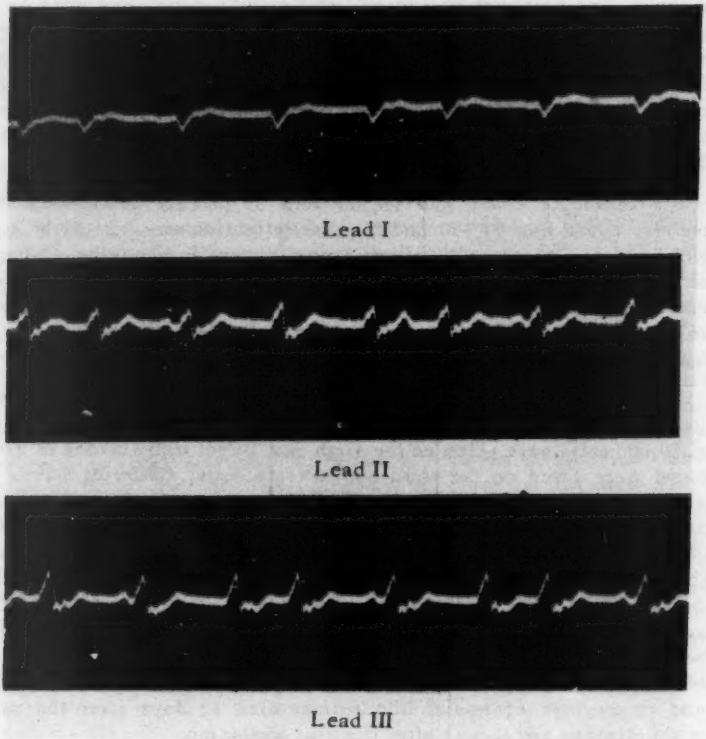

Figure 1 (case 1). ECG taken 11 days after onset of the disease.

(4) intracardiac thrombosis, left atrial appendage; (5) acute passive congestion and edema in all lobes of both lungs, the liver, and the spleen; (6) cloudy swelling of the liver, kidneys, and adrenal glands; and (7) bilateral toxic and granular degeneration of the kidneys and adrenal cortex was made.

Case 2. A 32-year-old soldier, visiting his family while on leave, noted pain and swelling in the right side of his pharynx, soft palate,

and right cervical region on 16 July 1950. He was given an injection of penicillin by his family physician who advised hospitalization.

On admission to this hospital on 17 July, he appeared acutely ill. His temperature was 102.6° F. His respirations were 24. His blood pressure was 114/74. There was marked swelling of his right peritonsillar area with displacement of his right tonsil past the midline. No areas of fluctuation were noted either in the tonsil or in the peritonsillar area. An ulcerated area 1 cm. in diameter, covered by a white membrane, was present on the medial surface of his right tonsil. His breath had a musty or fetid odor. The anterior cervical lymph nodes on the right were firm, tender, and enlarged. The one draining the tonsillar area was about the size of a walnut. A tentative diagnosis of peritonsillar cellulitis with cervical lymphadenopathy was made. By the next day the peritonsillar induration and swelling and the cervical adenopathy had increased markedly. His respirations were free, but he had difficulty raising mucus from the throat because of the pain and swelling. His peritonsillar area and tonsil remained firm with no fluctuation. Diphtheria, as well as a tonsillar abscess with rupture in the parapharyngeal space, were considered as possibilities. On 18 July cultures for *C. diphtheriae* were made from the ulcerated area of the tonsil, and the right tonsil and peritonsillar area were aspirated without evidence of an abscess.

The initial throat culture was negative for *C. diphtheriae*. His leukocyte count on admission was 14,450 with 54 percent neutrophils. His heterophil agglutination showed a partial agglutination in a dilution of 1:20. His urine showed a trace to 1 plus albumin and 5 or 6 red blood cells per high power field.

Treatment with penicillin, aureomycin, and streptomycin, begun on admission, was continued through the tenth hospital day. The swelling and induration of the right peritonsillar region, lymph glands, and soft tissues of the right side of the neck, continued to increase, reaching a maximum on the fourth hospital day. An incision was made in the edematous palate, but only edematous tissue, without evidence of localized pus formation, was found. The swelling gradually receded. The patient's temperature was only slightly elevated after admission. On the twelfth hospital day, he developed nausea and vomiting with acute pain in the precordial and left anterior thoracic regions which lasted for about 18 hours. A drop in blood pressure to 90/55 was, except for abnormalities in the ECG, the only cardiovascular abnormality noted at the time. The abnormalities in the first ECG consisted of sinus tachycardia, low amplitude of the T waves and S-T segment depression in the precordial leads.

Because of the unexplained thoracic and precordial pain and abnormalities in the ECG, the patient was transferred from the ear, nose, and throat section to the cardiovascular section. The thoracic pain and

minor electrocardiographic abnormalities persisted. On 15 August, a month after his illness began, and after all swelling of the throat had subsided, it was noted that he had difficulty swallowing and that water was being regurgitated through his nose. Careful examination of his throat revealed a paralysis of the right side of his palate and a loss of sensation in the right side of his pharynx. Neurologic examination revealed other abnormal neurologic findings and it was realized that in spite of the initial negative throat culture for *C. diphtheriae*, the clinical findings were those of a diphtheritic myocarditis and neuropathy. A spinal fluid examination showed a total protein of 65 mg. per 100 cc., 3 cells per cu. mm., no increase in globulin, and a 112210000 colloidal gold curve.

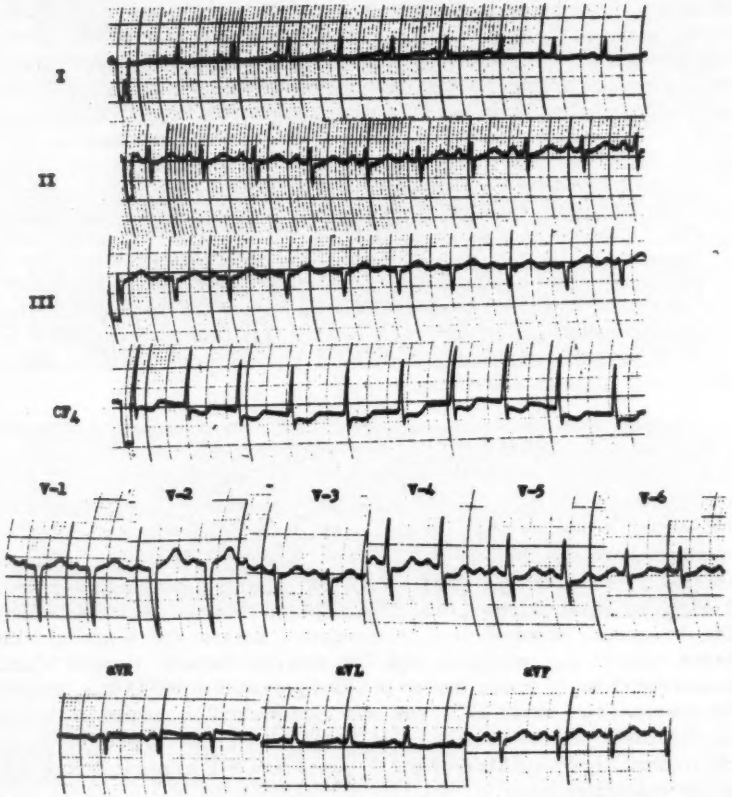

Figure 2 (case 2). Initial ECG of 2 August 1950 showing abnormalities of the T waves in leads aV_L and I and S-T segment depression in CF_4, V_4, V_5 and V_6. This ECG was taken during a period of precordial pain.

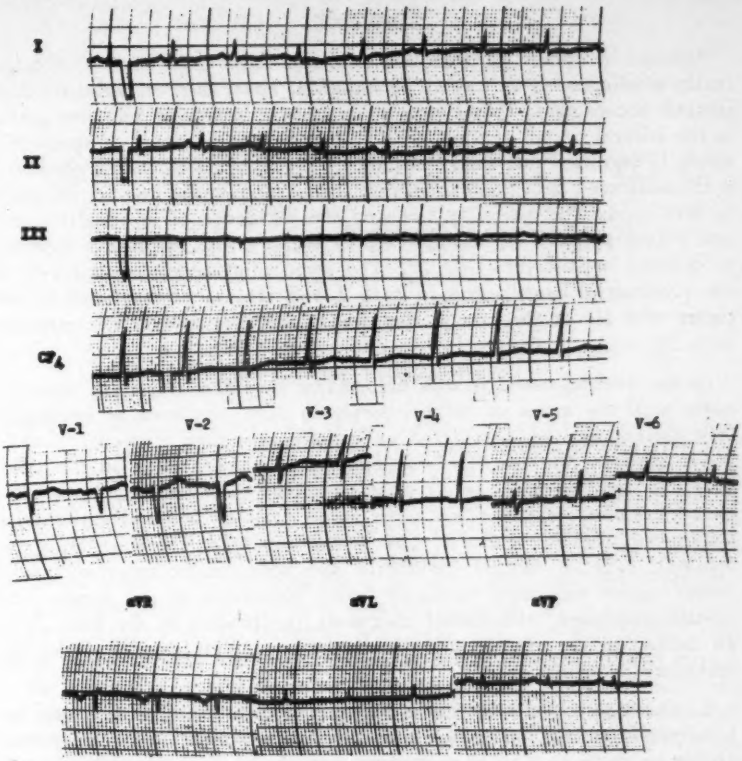

Figure 3 (case 2). ECG of 14 August 1950 showing slight terminal inversion of the T waves in leads I and II and decrease in the amplitude of T waves throughout the ECG.

Neurologic examinations during the following month revealed absence of the right knee jerk, external deviation of the right eye, absence of the deep tendon reflexes, and loss of vibratory sense over the fingers and toes. These neurologic abnormalities were slow in clearing. The RS-T segment and T-wave abnormalities persisted until the end of September (2 months after admission) but except for tachycardia, which persisted after months of convalescence, there were no other cardiac abnormalities. Six months after his initial illness he was returned to limited duty. Samples of serial ECG's are shown in figures 2 and 3. By 23 September the T waves and S-T segments were normal and they were still normal when the patient was seen on 2 February 1951. A final diagnosis of (1) diphtheria, faucial, peritonsillar; (2) myocarditis, diphtheritic; and (3) polyneuropathy, diphtheritic was made.

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COMMENT

Because of marked peritonsillar swelling, these 2 patients were originally misdiagnosed as having peritonsillar abscesses or cellulitis and treated accordingly. Unfortunately, in case 2 antitoxin was not given in the critical period of from 48 to 72 hours after the onset of symptoms and it is regretted that the established rule of giving antitoxin whenever it is considered necessary to culture for *C. diphtheriae* was not followed in this case. The mortality rate and the incidence of myocarditis and late polyneuropathy are much greater if therapy with specific antiserum is delayed beyond this time (7). The myocardial necrosis observed at the postmortem examination in case 1 was typical of that seen in patients who die at the end of the second week of diphtheritic myocarditis (8).

In the second case, it was unfortunate that the diagnosis was not made until the onset of palatal paralysis. The sequence of events in this patient may be considered as usual rather than atypical. The T-wave changes and the RS-T segment displacement seen in the ECG were the type of abnormality most commonly seen in diphtheria. Because antibiotic therapy had been given prior to hospitalization, the finding of negative cultures was to be expected. Because both the sporadic case of faucial diphtheria and peritonsillar infections from other causes may have moderate fever, ulceration of the tonsil, and pseudomembranes, differential diagnosis is difficult in the first 24 to 48 hours. In the treatment of peritonsillar infections, the following procedure is recommended:

1. Cultures should be made promptly from the throat lesions for *C. diphtheriae* and other organisms and an antibiotic sensitivity test should be made as a guide to therapy.

2. If antibiotics were given prior to initial examinations and initial culture, a negative culture for *C. diphtheriae* should be ignored.

3. If the lymphadenopathy or edema fails to respond to adequate antibiotic therapy in the first 24 to 48 hours of the disease, a diagnosis of diphtheria should be considered.

CONCLUSION

Myocarditis should be watched for as a complication in patients who have diphtheria or are suspected of having diphtheria.

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Group Psychotherapy in a Naval Neuropsychiatric Center

Evan L. Wolfe, *Psychologist (1)*

THE practical orientation of psychiatry in the naval service as in other services is toward the rehabilitation of men to a duty status. It must first be determined which patients can be returned to duty. Those who cannot be returned to duty are given treatment sufficient to meet their immediate needs and are, in most cases, discharged from the service or transferred to a veterans hospital. Many practical problems arise in dealing with these patients. Individual psychotherapy in sufficient amounts is rarely feasible because of the patient load and the rapidity of the turnover. Realizing this, it would appear that group psychotherapy could and should be used to a much greater extent in the treatment of these patients. An examination of the U. S. Naval Medical Bulletins since 1944 and of the U. S. Armed Forces Medical Journal indicates that few articles have been written concerning this problem *(2-5)*.

I believe, therefore, that it would be useful to describe some personal experiences in working with groups of psychiatric patients, all of whom have been considered sufficiently ill to be on maximum security wards and many of whom have undergone one of the somatic treatments. My primary aim in writing this article is to highlight some of the problems that occur in attempting to conduct group psychotherapy in a naval setting and to make a few suggestions about how to treat such problems.

(1) U. S. Naval Hospital, Oakland, Calif.

(2) Dynes, J. B., and Hamilton, F. J.: Group therapy of psychiatric war casualties. U. S. Nav. M. Bull. 44: 549-557, Mar. 1945.

(3) Teicher, J. D.: Experiences with group psychotherapy. U. S. Nav. M. Bull. 44: 753-755, Apr. 1945.

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DIFFICULTIES IN INSTITUTING GROUP THERAPY

Many problems are encountered in getting group therapy under way. One of the foremost is the attitude of the potential group leader toward group psychotherapy. The group approach has sometimes been viewed as a poor substitute for individual psychotherapy and hardly worth the effort, even though individual psychotherapy may not be available for most patients. Even more important, the group leader must face certain personal anxieties in working with a group of patients. These anxieties may not be aroused at all in individual psychotherapy or if they are they may be quite different. Group pressures and group reactions directed toward the group leader can be extremely threatening. This may also be true of the ambivalent attitudes of one patient toward another. A vague, almost unconscious awareness of such anxieties has often prevented staff members from attempting to work with patients in a group situation. The attitude of the leader toward group psychotherapy must be worked out by the leader himself through frequent consultation with his supervising psychiatrist and in the light of his self-understanding and insight into his own anxieties.

Another problem which is difficult to obviate in our setting is that of selection. Patients with similar psychopathology are not often on the same ward. Because at this hospital patients are segregated on wards according to their behavior patterns, acute and chronic schizophrenics, psychopaths, anxiety neurotics, and patients with practically every other type of psychiatric disorder may be found on the same ward. All types classified from the prognostic point of view may also be found. Finally, from the point of view of appropriateness for further treatment at a Veterans Administration hospital or of discharge to civil life, all types may be found on the same ward. This makes it difficult to form groups with similar orientation, symptoms, or problem complexes. This situation can be alleviated somewhat by a partial selection and screening of the ward population.

A third problem to be faced in our setting is the time element. Because of the exigencies of the military service and the many administrative considerations beyond the control of the psychiatric service, there are frequent interward and interhospital transfers. Patients remain on a ward for an indeterminate and highly unpredictable length of time. The time limit can be controlled partially by arranging with the particular psychiatrist administratively responsible for the ward, whenever possible, to keep a patient on a ward at least long enough for minimal therapy.

SELECTION

It is impossible to employ the usual criteria for selection found in most of the group therapy reported because of some of the limiting factors mentioned above. Nevertheless, some selection is possible and is important not only in formulating the goals of group psycho-

therapy in a naval setting, but also in determining the method to be used. A group of between 7 and 9 patients seems ideal *(6)*. Because of time and other limitations, we have found it necessary at times to select patients after only a quick perusal of their health records, a short interview with the patient, and a brief consultation with the ward psychiatrist. Thus, there is seldom opportunity to get real homogeneous groups.

Attempts have been made, however, to select such a group with respect to the following criteria: (1) some ability or potentiality to verbalize with more or less rationality, (2) freedom from severe psychopathic traits, (3) freedom from extreme confusion or agitation, and (4) freedom from regular overt hallucinatory or delusional experiences. Other factors are also considered. An attempt is made to select patients with similar problems in order to alleviate to some extent the feeling of "aloneness," so common among those with emotional illness. Some attempt is also made to select schizophrenics who are in partial remission, patients who are being maintained on subcoma insulin treatment, and those with milder types of psychoneurotic disorders. One reason for concentrating on these types is that it is hoped that the sessions will prepare the patients for their adjustment to future open-ward status.

GOALS

It is important at the outset for the group leader to go over very carefully with the supervising psychiatrist the goals that he has in mind for his group and to make them as explicit as possible. Following this procedure helps the group leader to orient himself to the task at hand and constantly to evaluate and re-evaluate his methods in the light of these goals. Experience has demonstrated time and again that it is necessary for the leader to modify or change both his methods and his goals many times as a result of the discussions with his supervisor of the spontaneous group dynamics as they emerge or in view of the ever-changing personnel of the group.

For example, spontaneous group discussion may focus attention on special problems about hospital administration, rules, regulations, and procedure. At such times the goals may have to be altered toward information giving, clearing up misconceptions, raising ward morale, and attempting to increase the patient's adjustment to his ward. At other times the group may focus on such matters as adjustment to an open ward, transfer to another hospital, return to duty, or ultimate discharge. Thus the goal is primarily one of increasing the patient's understanding of his adjustment in his present and immediate future situations, always keeping in mind that the specific goals must be constantly altered and revised.

(6) Foulkes, S. H.: Introduction to Group-Analytic Psychotherapy. Wm. Heinemann, Ltd., London, 1948. pp. 55-56.

It is important to be aware not only of flexible group goals, but also of individual ones. Realizing that selection procedures are not rigid and that a wide variety of personalities are present in the group, one can still have modest goals for individual members of the group. The goal for one patient may be nothing more than information giving in order to reduce anxiety caused by ignorance, misconceptions, or rumor; for another it may be catharsis and ventilation of disturbing emotional attitudes in a permissive atmosphere; for a third it may be the support of positive growth strivings or of a budding independent attitude about which the patient may display much ambivalence; and for other patients it may be insight into the relationships between the problems faced on closed wards and those faced on open wards or in civil life.

Time and again we have seen patients achieve their individual goals on one level, integrate them partially and move on to higher goals, all the while reinforcing and strengthening the goals previously achieved on a lower level. This is a continuous process going on in all group members. Observing this aspect of group behavior is a fascinating way of evaluating the benefits of group psychotherapy.

STRUCTURING

Orientation and structuring needs to be done frequently in the group because (1) the group changes so constantly, (2) many of the patients have great difficulty in concentrating, and (3) it is essential that the patient not be sidetracked from the goals that have been determined on and that the needs of most of the group rather than any one patient be concentrated on.

Often structuring can be accomplished by appealing to patients who have been in the group for several weeks. They can be asked to express the purpose of the group as they see it and in their own words. This is often much more effective than when it comes from the group leader. This is particularly true when the group members are reticent, negativistic, unable to concentrate, overly verbose, intimidating, or have gross misconceptions based on their own personal needs as to the purpose of the group.

Structuring should usually be in rather broad, general terms with emphasis on the group goals. This has the advantage of a wide enough latitude to cover some of the major problems of every member of the group without being so nonspecific as to leave the group completely unoriented. An example of a typical structuring is the following:

> "We are here to explain and discuss the ward rules, regulations, and procedures, to give out information about what happens to you during your stay here at the hospital, and to answer questions about your treatment and why you are here. Another purpose for meeting is to discuss the common problems of everyday living that all of us are faced with—our adjustment to the people with whom we work and live—our friends, relatives, superiors, and inferiors.

We also discuss what things will be like when we move to the open wards, or when we go back to duty, or return to civil life. Finally, we are here to discuss any subject or problem that anyone brings up which the group as a whole believes would be worth discussing."

Not all these ideas are presented at any one time, but the group leader attempts in a gradual way to orient the group to the above-mentioned problems. This type of structuring is quite general and it would be necessary to repeat various phases of it during the succeeding sessions, but the particular subject discussed is not the most important aspect. More important is the opportunity to stimulate group interaction, to promote emotional catharsis, to increase socialization, to decrease feelings of isolation, and to produce a positive attitude toward treatment and the next step in the recovery program.

LEADERS

The chief psychiatrist is the supervisor of group psychotherapy at this hospital. Frequent consultation with him as well as the ward psychiatrist and/or other staff members is imperative. It is also advantageous to submit frequent written reports or summaries of certain aspects of the group discussions and to use these in the supervisory sessions. Recordings of the discussions can aid the supervisor in fulfilling his function more adequately, but participation by another staff member as an observer in the group seems to be the best way to get an accurate picture of what goes on in group psychotherapy. At this hospital, the psychologist has usually assumed the role of the group leader, but we have also had groups in which the ward psychiatrist has acted as the group leader, while the psychologist was the observer. This article deals primarily with the former arrangement.

The group leader's task is to explain and to emphasize the purpose of the group to new members, to introduce new members to the group, to answer technical questions, to aid in intragroup communication, to reflect feelings, to orient the group toward its problems as a group, and, perhaps most important, to act as a catalytic agent. The psychologist has the advantage of being in a nonadministrative role and of functioning as a civilian. On the other hand, he may not always convey the prestige and authority that the ward psychiatrist often does.

In the type of group therapy in which the psychologist assumes the role of group leader we have found it advantageous to have the ward psychiatrist sit in the group as an observer, participant, and technical expert because he can then evaluate the results and increase the group leader's sensitivity and awareness of the group's needs. We have found it important to take from 30 to 60 minutes after a session to discuss with the ward psychiatrist the group dynamics of the session. The meaning of what goes on in a group thus becomes clearer and more objective. The group leader's observations can be checked for validity

against another person's observations. They can be particularly valuable when the other person is both a participant as well as a co-observer. When the group leader verbalizes his hunches and intuitions and exhibits them to the uncompromising critical light of another's scrutiny, they become either scientifically validated observations or they fall by the wayside as unsound premises. If the group leader does not spend a minimal time analyzing group dynamics with another participant-observer, he works partially in the dark. There is little motivation for him to do much of this analysis on his own. He is inclined to take the easy way out, to become intellectually lazy, and to overlook many vital and important issues even though consulting his supervisor regularly.

When the ward psychiatrist is an observer of the group discussions it further emphasizes his own interest in and approval of the group therapy sessions as part of the treatment program. This provides reassurance not only to the members of the group including the group leader, but also to other staff members of the ward. They accord group psychotherapy its legitimate place in the treatment program and act accordingly. The ward psychiatrist is by far the best qualified person to answer questions regarding ward administration and treatment procedures. Because this is a subject of great interest in our groups, it is important that such information be obtained from a primary and reliable source, i. e., "straight from the horse's mouth." The ward psychiatrist can also support patients in the group, reflect feelings, or clarify verbalizations when for some reason the psychologist is unable to do so. There are times in group discussions when purely personal or situational factors may prohibit him from fulfilling these functions. In such situations another person may be able to support the group leader. Later on, the factors involved can be thoroughly examined and discussed in the postsession evaluation.

Because the ward psychiatrist has officer status and is in a position of administrative authority, his presence may inhibit free discussion. This is especially true during the early stages of group formation or when new members enter the group. This is a problem that must be faced realistically and can often be used therapeutically. The ward psychiatrist must accept the resistance that is bound to come and must survive the "testing out" phase that will occur almost as soon as the group is formed. If the group's resistance in this connection is immediately recognized and accepted, it constitutes only a minor barrier. The advantages seem to far outweigh the temporary disadvantages and sometimes the resistance can easily be turned to therapeutic use.

An astute and observing group leader can often maneuver discussions in such a way that any or all of the patients can aid him by supporting each other, reflecting and clarifying feelings, making interpretations, and promoting insight. At various times any patient may spontaneously

assume one or more of these roles. These healthy, natural, and spontaneous reactions can and should be exploited in every way possible. At times, through experience, education, training, or psychologic sensitivity, patients may have the most accurate information available about a topic of group concern. Individual members should be encouraged to impart this information to the group. At other times the group leader may detect a "supportive" attitude, emotional overtone, or verbalization of one patient for another. This, too, should be stimulated and encouraged.

Because mentally ill people are often peculiarly sensitive to another patient's needs, a patient may be in a better position to clarify the meaning of another patient's verbalizations or behavior. The group leader's awareness of the capacity for such sensitivity is one of the most potent aspects of group therapy. It increases group morale tremendously by fostering positive growth trends in patients by stimulating their desire to help each other and by encouraging them realistically to examine their own and each other's attitudes and goals.

SPECIAL PROBLEMS

The matter of required participation is sometimes difficult to decide. Flexibility must be the key to this problem although in general the group members are expected to attend the sessions regularly until they leave the ward just as they are expected to meet all the other prescribed ward routines. Each member is free to talk or to remain silent as he sees fit, but his physical presence is required unless there is a valid reason for his absence. This point of view may seem arbitrary, but is adopted because the patients are selected on the basis that they will benefit from the discussions and because they are initially screened to eliminate those who will threaten other members too much or those who will be too greatly threatened themselves. There are times when patients are not able to make a rational decision about their participation in the group. Resistance to this requirement comes up readily and immediately can become a topic for group discussion.

Often insight into the nature of resistance to this rule and to ward routine in general is obtained. It is especially gratifying when a member of the group facilitates this insight. Often such a requirement readily fits into other aspects of service requirements and is accepted as such by the patients. When it is not accepted, the relationship between resistance to this rule and attitudes about discipline in general can easily be explored. Occasionally, in spite of screening, a patient who attempts to use the sessions for his own personal manipulation to the detriment of group morale and to the point where the group is unable to work constructively may be included in the group. When this situation becomes too acute, the patient may have to be barred from the group discussions. At times the group leader may hesitate to take what may seem like a drastic step to him because of his own guilt feelings, or

because he may interpret the difficulty as a reflection of his poor selection, or as a manifestation of his inadequacy as a group leader. Nevertheless, it is only realistic to admit an error in clinical judgment as to the suitability of patients for group therapy or to acknowledge fallibility in dealing with some of the problems that arise. The group leader can check his judgment on this and similar matters by taking them up with his supervisor.

Often other members of the group are relieved when the group leader takes such a step. Far from looking on it as a reflection of his weakness, they may be quite reassured by the knowledge not only that the group leader can honestly acknowledge a mistake, but also that he can take positive action to rectify such errors. This can be quite reassuring to them. It is the same principle that is involved when a therapist sets realistic limits for a patient in individual therapy.

Another important problem often encountered is the group leader's need to protect individual group members from erotic or hostile expressions from other group members. The latter expressions seem to occur more frequently, but disguised and symbolic erotic expressions also occur. Because of countertransference feelings, the group leader may feel the need to protect a patient from the emotional outbursts of others. This countertransference must be clearly recognized and the group leader's feelings in such situations must be understood. At times such support is necessary, particularly when a patient's ego defenses are weak, but many times such support, far from being reassuring, has a debilitating effect on both the patient involved and the group as a whole. At such times the patient may believe, and often with good reason, that the group leader has little confidence in him.

Even more crucial is the fact that such alleged support and focusing on individual needs often inhibits the very process that group therapy is designed to stimulate; namely, group interaction on a highly charged emotional level. Such feelings need to be verbalized and brought out into the open before they can be examined and understood. Too much support and diluting of emotionally charged material, either by ignoring emotionally charged statements or by rephrasing them into less emotionally charged words, inhibit this process and are often the result of the group leader's own anxieties about how to deal with emotionally loaded situations.

Still another problem is that of the necessity for a systematic review of the material covered in previous sessions as a prelude to discussion. We are gradually placing less emphasis on this. Too much review fosters an already well-established tendency to let the group leader conduct the discussions and to avoid participation and responsibility. Some believe that a review reinforces what patients learn from previous sessions, but it seems probable that the value of such reinforcement can be overestimated. We believe that what little reviewing is done

should be directed toward re-emphasizing the purpose of the group, clarifying emotional attitudes, and paving the way for further emotional catharsis. Aside from these points it has little positive value and can be potentially disruptive.

Although there are many other special problems which have not been mentioned, the most pertinent have been discussed in an attempt to highlight the problems which make it difficult to conduct group psychotherapy in the Navy.

CONCLUSIONS

A lack of time, a feeling that competent people are not available, administrative difficulties, skepticisms as to the value of group therapy, and, most of all, and underlying all of these, anxieties on the part of the group leader have made potential leaders reluctant to adopt this form of therapy in the Navy. It is hoped that this article has helped to clarify some of the difficulties that exist, has demonstrated how some of them can be obviated, and has encouraged those charged with the care and treatment of the emotionally disturbed to experiment with group psychotherapy under proper psychiatric supervision. The time and energy invested where this method has been used has reduced the length of stay on closed wards, eased the workload and emotional strain on the psychiatric ward staff, and increased the morale of the staff by enhancing their feeling of a job well done.

BOOK REVIEWS

Working Programs in Mental Hospitals, Proceedings of the Third Mental Hospital Institute held under the auspices of the Mental Hospital Service of the American Psychiatric Association, Kentucky Hotel, Louisville, Ky., October 15-18, 1951, edited by *Daniel Blain,* M. D., Medical Director, A. P. A., with the Staff of the A. P. A. Mental Hospital Service. 203 pages. American Psychiatric Association, Washington, D. C., publisher, 1952. Price $2.50.

This book gives a comprehensive account of the many informal "down-to-earth" discussions carried on by the Mental Hospital Institute. Except for 1 prepared paper the book is a report of free discussion of topics from the floor following a brief introduction by the discussion leaders. Those attending the sessions included doctors (mainly psychiatrists), nurses, business managers, board representatives, budget officers, members of boards of control, planning groups, and others from all over the United States and Canada. The following subjects were discussed: (1) needs of mental hospitals, (2) hospital standards, (3) ward personnel, (4) ward management, (5) economy of operation,

(6) hospital-university relationships, (7) standards for schools and homes, (8) the sexual psychopath, (9) food preparation, (10) research, (11) group methods, (12) the aging process, (13) intensive treatment, (14) patient's relatives, and (15) appropriations. This book should be read by all psychiatrists and psychiatric nursing supervisors, and would be of great interest and value to anyone with administrative responsibilities in a mental hospital.—*Col. F. R. Drake, MC, U. S. A.*

Advances in Pediatrics, Volume V. Editor, *S. Z. Levine,* Cornell University Medical College, New York. Associate Editors: *Allan M. Butler,* Harvard Medical School, Boston; *Margaret Dann,* Cornell University Medical College, New York; *L. Emmett Holt, Jr.,* New York University College of Medicine, New York; and *A. Ashley Weech,* University of Cincinnati College of Medicine, Cincinnati. 273 pages; illustrated. The Year Book Publishers, Inc., Chicago, Ill., 1952. Price $7.

The lapse of over 2 years between the publication of volumes IV and V of this series is explained by an interim change in publishers. The present volume maintains the high standards established by its predecessors regarding choice of content and contributors.

"Advances in the Treatment of Bacterial Meningitis" by Dr. Alexander covers therapy and choice of therapeutic agents extensively. The author's treatment of the problem of optimal therapy is particularly valuable. "The Nephrotic Syndrome" by Dr. Barnett et al. gives the latest concepts of the treatment of this condition. "Iron Metabolism in Infants and Children" by Dr. Smith presents recent advances in this often poorly understood field. The importance of and reasons for continuing treatment after the return of the hematologic findings to normal is only one of the fascinating facets which are discussed. Foreign contributions include "The Relation of Vitamin K Deficiency to Hemorrhagic Disease of the Newborn"; "BCG Vaccination"; and "Angiocardiographic Studies in Children." The latter is replete with roentgenographs and illustrations showing the technics used. "BCG Vaccination" is a most complete presentation of a subject often slighted in the domestic literature. Reasons for vaccination and a discussion of the preparation of the vaccine, together with the duration of the immunity conferred are presented in full. The presentation of hemorrhagic disease of the newborn covers, among other things, the physiology of prothrombin variation during infancy and the effect of vitamin K prophylaxis.

Extensive bibliographies are given. The volume should be a valued addition to the library of every pediatrician.

—*Capt. F. C. Biebusen, MC, U. S. A.*

Meningitis and Hepatitis Due to Infectious Mononucleosis

Murray Herman, *First Lieutenant, U. S. A. F. (MC)* (1)

INFECTIOUS mononucleosis is a disease occurring principally in children and young adults and believed to be caused by a filtrable virus. It is usually benign and has been divided into three main types (2): (1) glandular or Pfeiffer type characterized by lymphadenopathy, usually of the cervical nodes but frequently involving the axillary and inguinal nodes as well, and often accompanied by a palpable spleen; (2) pharyngeal type characterized by tonsillitis or pharyngitis; and (3) febrile type usually diagnosed as a fever of unknown origin.

The diagnosis is based on three main criteria (3), any two of which are sufficient to establish the diagnosis: (1) cervical lymphadenopathy, (2) increase in mononuclear leukocytes, and (3) positive heterophil agglutination test.

Hepatitis is a frequent complication of infectious mononucleosis but encephalitic and/or meningitic involvement is less commonly seen. In a review of the recent literature since 1941, 10 cases (2-7) of neurologic involvement presumably due to infectious mononucleosis were noted. Three of these patients died. The following case which demonstrated hepatic as well as central nervous system involvement was recently observed at this base. No other report of this combination has been found.

(1) Wichita Air Force Base, Wichita, Kans.

(2) Peters, C. H.; Widerman, A.; Blumberg, A.; and Ricker, W. A., Jr.: Neurologic manifestations of infectious mononucleosis, with special reference to Guillain-Barré syndrome. Arch. Int. Med. 80: 366-373, Sept. 1947; correction 81: 111, Jan. 1948.

(3) Paige, B. F.: Infectious mononucleosis. Canad. M. A. J. 62: 173-176, Feb. 1950.

(4) Landes, R.; Reich, J. P.; and Perlow, S.: Central nervous system manifestations of infectious mononucleosis; report of case. J. A. M. A. 116: 2482-2484, May 31, 1941.

(5) Vaughan, S. L.; Regan, J. S.; and Terplan, K.: Infectious mononucleosis complicated by spontaneous rupture of spleen and central nervous system involvement. Blood 1: 334-338, July 1946.

(6) Bickel, G.; Mach, R. S.; della Santa, R.; and Ducommun, P.: Les formes nerveuses de la mononucléose infectieuse. Schweiz. med. Wchnschr. 78: 938-941, Sept. 25, 1948.

(7) Graham, S. D.; Schwartz, W. H.; and Chapman, W. L.: Infectious neuronitis complicating infectious mononucleosis. U. S. Nav. M. Bull. 49: 914-919, Sept.-Oct. 1949.

CASE REPORT

On 27 October 1951, a 23-year-old man noted a bilateral throbbing temporal and suboccipital headache aggravated by coughing, sneezing, or sudden head movements. This was accompanied by chills, fever, nausea, and low back pain, but no focal weakness. Because his symptoms grew progressively worse and poliomyelitis was suspected, he was admitted to the hospital on 28 October. He had had mild nasal congestion and burning on urination for several weeks and attacks similar to his present illness at irregular, infrequent intervals since 1946. These episodes always occurred at night and had previously subsided by the following morning. He had not sought medical attention for them. On admission he did not appear acutely ill. His temperature was 99° F.; his pulse was 88; his respiration was 18; and his blood pressure was 100/55. A few small nontender posterior cervical nodes were palpable and he had a 2 to 3 plus nuchal rigidity. His urine was cloudy and amber with a pH of 6 and a specific gravity of 1.013. The sediment showed from 10 to 15 pus cells and an occasional erythrocyte per high power field. The leukocyte count was 12,950 with 58 percent segmented forms, 2 percent juvenile forms, 7 percent stab cells, and 33 percent mature lymphocytes. A spinal tap on admission revealed a pressure of 350 mm. of water, a cell count of 900 lymphocytes, 78 mg. of protein per 100 cc., 138 mg. of glucose per 100 cc., and was reported sterile to culture after 6 days. Blood drawn the day following admission for agglutination studies for mumps, lymphocytic choriomeningitis, equine encephalitis, and St. Louis encephalitis were all reported as negative by the Kansas State Department of Health Laboratory.

A regimen of hot packs, salt tablets, and 300,000 units of penicillin daily was started. The patient's course was afebrile and asymptomatic with demonstrable lessening of his nuchal rigidity until 3 November when he complained of epistaxis, anorexia, nausea, lightheadedness, and generalized malaise. Physical examination on that date revealed his neck to be supple and his temperature to be 100° F. There was pain on percussion over the right lower portion of his chest and tenderness in his right upper abdominal quadrant. No abdominal masses were palpable. His leukocyte count was 7,000 with 47 percent segmented forms, 3 percent eosinophils, 2 percent stab cells, and 48 percent lymphocytes. On 4 November his temperature reached 102.5° F. and he vomited 3 or 4 times. The liver area was still tender. A blood culture drawn on this date revealed no growth. His urine was positive for bile and urobilinogen was present in a dilution of 1:30. On 5 November his temperature was 102° F. His urine was again positive for bile and urobilinogen was positive in a dilution of 1:30. The serum bilirubin was found to be: indirect, 0.45 mg. per 100 cc.; direct, 0.25 mg. per 100 cc., 60 percent prompt. Bromsulphalein retention was 68 percent in 5 minutes and 8.2 percent in 30 minutes; thymol turbidity was 2.5 units; cephalin-cholesterol flocculation was negative in 48

hours; alkaline phosphatase was 2 units; and the total serum protein was 8.35 grams (albumin 5.59 grams and globulin 2.76 grams). On 6 November he was somewhat improved although he was still febrile and the tenderness over the liver area persisted. The spinal fluid revealed a cell count of 42 lymphocytes and 1 polymorphocyte, 82 mg. of glucose per 100 cc. and 685 mg. of chloride per 100 cc., a negative Wassermann test, and a colloidal gold curve of 0000000000. There was no pellicle formation and the fluid was negative to culture. Bile was still present in the urine and urinary urobilinogen was positive in a dilution of 1:100.

In view of the bile and the rising urobilinogen titer in the urine, it was believed that this case of meningitis of unknown cause was being complicated by a hepatitis also of unknown cause. A high protein, high caloric, high vitamin diet; strict bed rest; and methionine and crude liver extract parenterally were prescribed. On 8 November a leukocyte count and a heterophil agglutination were requested. The leukocyte count was reported as 14,000 with 27 percent polymorphocytes, 66 percent lymphocytes, 4 percent monocytes, and 3 percent eosinophils; 40 percent of the leukocytes were reported as abnormal, large, young lymphocytic forms. The heterophil antibody test was positive in a dilution of 1:1,792, indicating infectious mononucleosis.

The course was febrile with daily temperature elevations up to 102.5° F. until 11 November, following which he remained afebrile. On re-examination many slightly tender, small to moderate-sized, right posterior cervical lymph nodes, right axillary nodes, and a single large right inguinal node were palpated. At no time was the patient's spleen palpable. Bile was present intermittently in his urine until 12 November and by 6 November his urobilinogen had returned to normal. On 21 November he was given a 21-day convalescent leave during which he was asymptomatic and gained 10 pounds. At the end of this leave all his adenopathy and liver tenderness had disappeared, but on 14 December he had a 3 plus cephalin-cholesterol flocculation in 48 hours and a thymol turbidity of 14. He was discharged to duty on 5 January 1952. by which time all liver function tests had returned to normal and he had gained another 5 pounds. His leukocyte count at the time of discharge was 12,900 with 70 percent polymorphocytes, 29 percent lymphocytes, and 1 percent eosinophils. When last seen on 14 January he was feeling well; his liver function tests were all normal; and his heterophil agglutination test was positive in a dilution of 1:14.

Comment. This patient had a meningitis of unknown cause. The cervical adenopathy was ignored initially because meningeal involvement caused by the agent of infectious mononucleosis was not thought of. Other common causes of meningitis and encephalitis were effectively ruled out by appropriate agglutination tests. The abnormal leukocyte

count and strongly positive heterophil agglutination proved the diagnosis of infectious mononucleosis. It is interesting to speculate how many cases of so-called meningism, Guillain-Barré syndrome, nonspecific meningitides, et cetera, are due to infectious mononucleosis.

BOOK REVIEW

The 1951 Year Book of Neurology and Psychiatry, November 1950-October 1951. Neurology edited by *Roland P. Mackay,* M. D., Professor of Neurology, University of Illinois; Attending Neuropsychiatrist, St. Luke's Hospital, Chicago; Psychiatry edited by *Nolan D. C. Lewis,* M. D., Director, New York State Psychiatric Institute and Hospital; Professor of Psychiatry, Columbia University. 556 pages; illustrated. The Year Book Publishers, Inc., Chicago, Ill., 1952. Price $5.50.

In recent years there has been an increasing tendency to condense the voluminous medical literature in order that busy practitioners may keep abreast of modern trends and advances in their respective fields. To achieve this goal, the Year Book presents brief abstracts of publications during 1951 that are considered by its editors to represent progress in neurology and psychiatry. In general, this volume (and particularly the larger section on neurology) succeeds admirably in its purpose. Well-deserved attention is paid to new research in neurophysiology. This accent on neurophysiology dominates many of the abstracts and illustrates growing knowledge of the epilepsies and cortical function. Advances in neurosurgery, especially those which open new spheres of therapeutic interest to the neurologist, are included.

A smaller section on psychiatry is more limited in its scope because the articles selected for review were mainly those that emphasize an organic approach to mental disease. This is exemplified by the fact that only 4 pages are devoted to psychotherapy, as compared to 30 pages on psychosurgery. Perhaps such a disproportion indicates the minimal advances in psychotherapy during 1951. Yet psychotherapy, both in individual and group technics, is the major tool of most practicing psychiatrists.

The comments of the editors, given in small print at the conclusion of many abstracts, are a definite aid to orientation. Even more footnotes of this type would be desirable. The Year Book should be especially helpful to those psychiatrists who have drifted away from structural and physiologic concepts of the nervous system because of preoccupation with purely psychologic concepts and psychopathology.

—*Col. A. J. Glass, MC, U. S. A.*

Medical Débridement by Enzymatic Action[1]

Bruce F. Chandler, *Captain, MC, U. S. A.* (2)

TWO enzymes, streptokinase (SK) and streptodornase (SD), derived from hemolytic streptococci and the enzyme, trypsin, are at present under extensive clinical trial as aids in cleansing areas containing clotted blood, pus, or necrotic tissue. In a series of clinical and laboratory investigations of the hemolytic streptococci which began in 1932, Tillett and his coworkers (3-7) observed that broth cultures of streptococci could cause a rapid lysis of fibrin clots of normal human blood. This lytic property was due to an extracellular enzyme, first called fibrinolysin, and was secreted by the organisms into the culture medium during growth. This fibrinolytic principle was found in culture media from other bacteria, but hemolytic streptococci, especially the Lancefield group A and one strain of the Lancefield group C, were by far the most prolific producers of the enzyme. Subsequent studies by Milstone (8), Christensen (9), and Christensen and MacLeod (10) showed that this enzyme did not have a direct fibrinolytic

(1) The streptokinase-streptodornase used in this study was kindly supplied by the Lederle Laboratories and the crystalline trypsin was kindly supplied by the Armour Laboratories.

(2) Walter Reed Army Hospital, Washington, D. C.

(3) Garner, R. L., and Tillett, W. S.: Biochemical studies on fibrinolytic activity of hemolytic streptococci; isolation and characterization of fibrinolysin. J. Exper. Med. 60: 239-254, Aug. 1934.

(4) Tillett, W. S.: Occurrence of antifibrinolytic properties in blood of patients with acute hemolytic streptococcus infections. J. Clin. Investigation 14: 276-284, Mar. 1935.

(5) Tillett, W. S.: Fibrinolytic activity of hemolytic streptococci. Bact. Rev. 2: 161-216, Dec. 1938.

(6) Tillett, W. S.; Edwards, L. B.; and Garner, R. L.: Fibrinolytic activity of hemolytic streptococci. Development of resistance to fibrinolysis following acute hemolytic streptococcus infections. J. Clin. Investigation 13: 47-78, Jan. 1934.

(7) Tillett, W. S., and Garner, R. L.: Fibrinolytic activity of hemolytic streptococci. J. Exper. Med. 58: 485-502, Oct. 1933.

(8) Milstone, H.: Factor in normal human blood which participates in streptococcal fibrinolysis. J. Immunol. 42: 109-116, Oct. 1941.

(9) Christensen, L. R.: Streptococcal fibrinolysis; proteolytic reaction due to serum enzyme activated by streptococcal fibrinolysin. J. Gen. Physiol. 28: 363-383, Mar. 1945.

(10) Christensen, L. R., and MacLeod, C. M.: Proteolytic enzyme of serum; characterization, activation, and reaction with inhibitors. J. Gen. Physiol. 28: 559-583, July 1945.

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action, but instead activated a precursor of a fibrinolytic factor, present in the euglobulin serum fraction, called "plasminogen." Plasminogen is the inactive precursor of the active enzyme "plasmin" to which it is converted by SK. Plasmin then catalyzes the breakdown of the insoluble protein fibrin into several small soluble proteins and some large polypeptide fragments. This situation is analogous to that which takes place in the human stomach, where the inactive enzyme, pepsinogen, is converted by hydrochloric acid into active pepsin, which in turn catalyzes the breakdown of food protein.

During early studies on SK, it was found that injections of crude concentrates of this enzyme could cause liquefaction of purulent exudates as well as exudates of fibrinous and sanguineous types, and it was believed that other enzymes were present in the concentrates. In 1948, Sherry et al. *(11)* showed that the major constituent responsible for the viscosity of pus was desoxyribonucleic acid which comprised from 30 to 70 percent of the total solids of such exudates. By a specific histochemical staining technic (Feulgen method) the desoxyribose nucleoprotein was found to originate in the leukocytes of purulent exudates *(12)*. A desoxyribonuclease which catalyzed the breakdown of this material by depolymerization was then isolated from streptococcal filtrates and the enzyme called "streptodornase" *(13)*. In contrast to the indirect action of SK, SD does not need the presence of a serum factor because it acts directly on its substrates: Desoxyribonucleic acid with SD ⟶ nucleotides and nucleosides which with SD ⟶ purine and pyrimidine compounds.

When SD is introduced into purulent exudates, they promptly and visibly change to a thin fluid of low viscosity *(14)*. Furthermore, the enzyme is not destructive to normal tissue because it acts only on extracellular nucleoprotein or on the nuclei of degenerating cells *(15)*.

Trypsin, derived from the pancreas, is a proteolytic enzyme effecting the breakdown of proteins, denatured proteins, fibrin, mucin, peptones, and split protein products. The end products are simple polypeptides

(11) Sherry, S.; Tillett, W. S.; and Christensen, L. R.: Presence and significance of desoxyribose nucleoprotein in purulent pleural exudates of patients. Proc. Soc. Exper. Biol. & Med. 68: 179-184, May 1948.

(12) Simpson, R. E. H.: Source of desoxyribonucleoprotein fibrils in purulent exudates. Lancet 1: 110, Jan. 13, 1951.

(13) Tillett, W. S.; Sherry, S.; and Christensen, L. R.: Streptococcal desoxyribonuclease; significance in lysis of purulent exudates and production by strains of hemolytic streptococci. Proc. Soc. Exper. Biol. & Med. 68: 184-188, May 1948.

(14) Tillett, W. S., and Sherry, S.: Effect in patients of streptococcal fibrinolysin (streptokinase) and streptococcal desoxyribonuclease on fibrinous, purulent, and sanguineous pleural exudations. J. Clin. Investigation 28: 173-190, Jan, 1949.

(15) Sherry, S.; Johnson, A.; and Tillett, W. S.: Action of streptococcal desoxyribose nuclease (streptodornase) in vitro and on purulent pleural exudations of patients. J. Clin. Investigation 28: 1094-1104, Sept. (pt. 2) 1949.

and amino acids (16, 17). Trypsin is likewise innocuous to normal tissue because the serum contains both a specific trypsin inhibitor and several nonspecific inhibitory substances which protect viable tissue from its proteolytic effect. It is the enzyme most uniformly found in the excreta of the maggots which were once used in the medical debridement of osteomyelitic lesions.

METHODS OF USE

An SK-SD mixture is available commercially in sterile ampules containing 100,000 units of SK and 25,000 or 60,000 units of SD in the form of a white, water-soluble powder which remains stable for several months in the desiccated form. The powder may be dissolved in water or saline solution, or mixed with a water-soluble base such as lubricating jelly or aquaphor to form an ointment. Solutions of SK-SD are stable for only 24 hours and should therefore be made up just before use. The material in solution may be applied as a soak, with catheters, or with the use of a rubber dam. Penicillin and streptomycin may be mixed in the ointment or solution but aureomycin is too acid for this purpose. The incorporation of 1 percent tetracaine or ethyl aminobenzoate is helpful if, for example, there is an exposed nerve at the base of an ulcer or fissure. The enzymes in saline solution are especially suitable for intrapleural use by injection through a needle or a catheter.

Trypsin is available commercially in capsules containing 250 mg. The dry, white, water-soluble powder is stable indefinitely, but the enzyme in solution is stable for only about 3 hours and should therefore be prepared just prior to use. The enzyme is supplied commercially with a companion vial of 25 cc. of Sorensen's phosphate buffer for use as a diluent. The material may be dusted on in powder form, used in a wet dressing, applied through catheters, or with a rubber dam. The solution may also be injected intrapleurally through a thoracentesis needle or catheter. It may be mixed with penicillin or streptomycin for local use.

No systemic reactions to local use have been reported for either SK-SD or trypsin, but when SK-SD is given intrapleurally, a febrile response as high as 105.6° F. has been observed within from 6 to 12 hours. The patient may become anorexic or nauseated and may vomit. Prostration is usually present. A sensation of diffuse soreness over the chest wall in the area surrounding the site of injection may develop. These effects almost always disappear within 24 hours. The leukocyte count and sedimentation rate may rise slightly, but the urine

(16) Reiser, H. G.; Roettig, L. C.; and Curtis, G. M.: Tryptic débridement of fibrinopurulent empyema. In Surgical Forum of the 1950 Clinical Congress of the American College of Surgeons. W. B. Saunders Co., Philadelphia, Pa., 1951. pp. 17-25.

(17) Reiser, H. G.; Patton, R.; and Roettig, L. C.: Tryptic débridement of necrotic tissue. To be published.

and blood pressure remain unchanged. Trypsin, used locally, does not result in systemic reaction, but does cause a mild to moderate burning sensation. Used intrapleurally, a mild histamine-like reaction, which can readily be controlled by antihistaminic drugs, is frequently seen. Febrile responses of short duration which may reach 102° F. have also been observed. Both enzyme groups work best at an alkaline pH; SK-SD at from 7.3 to 7.6 and trypsin at 7.1. Fortunately, most purulent exudates are in this pH range, but the area to be debrided should first be tested with nitrazine paper and, if markedly acid, should be flushed with buffer solution.

CLINICAL RESULTS

These enzymes had their first clinical application in pleural disease. More recently they have been used in a great variety of clinical conditions *(18-22)*. Tillett et al. *(23)* first reported a series of 6 patients (4 with hemothorax or empyema, 1 with a maxillary sinusitis, and 1 with osteomyelitis of the hip) all treated with good results. Tillett et al. *(24)* later reported a series of 27 patients with hemothorax in 25 of whom the results with SK-SD treatment were good and in 2 of whom they were poor. Wright et al. *(22)* reported a series of 46 patients, 5 of whom had chest conditions; 39 improved on SK-SD therapy and 7 (of which 3 had chest conditions) showed no improvement. Gaensler and Strieder *(25)* reported 3 patients with hematomas complicating extrapleural pneumothorax, all successfully treated with SK-SD. The largest series to date is that of Miller et al. *(20)* who treated 80 out of 85 patients (with a variety of conditions) successfully with SK-SD.

Trypsin has been used by Reiser et al. *(16)* in 7 patients with empyema, with 6 successes and 1 failure. Reiser et al. *(17)* have subsequently used the enzyme on infected amputation stumps, hematomas, chronic osteomyelitis (with little success), varicose ulcers, and decubitus ulcers.

(18) Cathie, I. A. B.: Streptomycin-streptokinase treatment of tuberculous meningitis. Lancet 1: 441, Mar. 12, 1949.

(19) Hazlehurst, G. N.: Streptokinase-streptodornase in treatment of suppurative tuberculous adenitis. In Surgical Forum of the 1950 Clinical Congress of the American College of Surgeons. W. B. Saunders Co., Philadelphia, Pa., 1951. pp. 439-442.

(20) Miller, J. M.; Ginsberg, M.; Lipin, R. J.; and Long, P. H.: Clinical experience with streptokinase and streptodornase. J. A. M. A. 145: 620-624, Mar. 3, 1951.

(21) Read, C. T., and Berry, F. B.: Utilization of streptokinase-streptodornase in patient with hemopneumothorax and patient with postpneumonectomy sanguineous coagulum. J. Thoracic Surg. 20: 384-392, Sept. 1950.

(22) Wright, L. T.; Smith, D.; Rothman, M.; Metzger, W. I.; and Quash, E. T.: Use of streptokinase-streptodornase in certain surgical conditions. J. Internat. Coll. Surgeons 15: 286-289, Mar. 1951.

(23) Tillett, W. S.; Sherry, S.; Christensen, L. R.; Johnson, A. J.; and Hazlehurst, G. N.: Streptococcal enzymatic débridement. Ann. Surg. 131: 12-22, Jan. 1950.

(24) Tillett, W. S.; Sherry, S.; and Read, C. T.: Use of streptokinase-streptodornase in treatment of postpneumonic empyema. J. Thoracic Surg. 21: 275-297, Mar. 1951.

(25) Gaensler, E. A., and Strieder, J. W.: Streptokinase-streptodornase in treatment of extrapleural hematoma complicating extrapleural pneumothorax. Am. Rev. Tuberc. 63: 547-555, May 1951.

TABLE 1. *Results of treatment of 67 patients with enzymes*

Diagnosis	Number	Results	
		Good	Poor
Patients treated with SK-SD			
Compound fracture with exposed bone	20	20	0
Ulcers in peripheral vascular disease	11	11	0
Infected amputation stump	7	7	0
Frostbite with gangrenous digits	5	5	0
Decubitus ulcer	3	3	0
Chronic tuberculous pleurisy	2	0	2
Hemothorax with clotting	1	1	0
Hydropneumothorax	1	0	1
Unexpanded lung following removal of cyst	1	0	1
Osteomyelitis	1	1	0
Soft tissue infection associated with carcinoma	1	0	1
Total	53	48	5
Patients treated with trypsin			
Infected amputation stumps	5	5	0
Osteomyelitis	5	0	5
Empyema	4	0	4
Total	14	5	9

At this hospital, these enzymes had been used in the treatment of 67 patients as of 8 October 1951. The types of patients treated and results are shown in table 1. We have been unable to duplicate the results of others in the use of these enzymes in chest disease, with the exception of the 1 patient with clotted hemothorax who responded most gratifyingly to treatment with SK-SD and was spared a surgical decortication. The other patients had conditions of much longer duration than his (all were more than 6 weeks) and too much fibrous tissue may already have formed to allow the enzymes to do their work properly. Most of these patients required decortication and the time spent and discomfort caused the patient by giving him the enzymes were to no avail. It may be unwise to attempt enzymatic débridement in any patient with empyema or other chest condition of over 1 month's duration, although various authors have reported success in chest conditions of up to 6 months' duration.

CASE REPORTS

Case 1. A 19-year-old man was wounded in action in Korea on 14 February 1951 by a bullet piercing his right arm and entering the right side of his chest. A right hemothorax developed and he was evacuated to the zone of the interior on 21 February without a thoracentesis having been done. His course was slightly febrile and penicillin had been given. He was admitted to this hospital on 27 February. Figure 1 shows a roentgenogram of his chest prior to treatment. A thoracentesis

Figure 1 (case 1). Roentgenogram taken 3 March 1951 showing chest 2 days prior to instillation of SK-SD solution. Figure 2 (case 1). Roentgenogram taken 6 May 1951, almost 2 months after completion of enzymatic therapy, showing a chest normal except for obliteration of the right costophrenic angle.

on 2 March resulted in the removal of only 200 cc. of dark brown fluid containing small clots which repeatedly plugged a 17-gage needle. An instillation of 100,000 units of SK and 60,000 units of SD dissolved in 10 cc. of saline solution into the pleural cavity was given on the following day after obtaining only 15 cc. of fluid by thoracentesis. Aspirin was given in doses of 0.66 gram every 4 hours starting on 4 March to help allay the febrile response to SK-SD. The chest was fluoroscoped before and after each thoracentesis. In the next 3 days, 1,020 cc. of thin, brown fluid were withdrawn from the pleural cavity. Temperature peaks up to 103.6° F. were noted. The patient was nauseated, anorexic, and had a localized pain in the chest. On 9 March another injection of SK-SD was given and an additional 200 cc. of fluid was subsequently withdrawn. Roentgenograms of the chest revealed improvement (fig. 2) and the patient began to gain weight and strength.

Case 2. A 25-year-old man developed rhinitis and a cough in October 1950. In November he noted weight loss and transient pains in the right side of his chest. On 24 December the chest pains recurred and a right pleural effusion was found. Three thoracenteses were done and a straw-colored fluid removed. The patient was admitted to this hospital on 16 January 1951 and a thoracentesis on that day yielded 200 cc. of straw-colored fluid. All studies for tuberculosis were negative. Roentgenograms showed a diffuse homogeneous density overlying the lower portion of the right lung. No fluid was obtained by other thoracentesis and 100,000 units of SK with 60,000 units of SD were injected on 1 February. The patient's temperature rose to 105° F. On the following day 160 cc. of a dark brown fluid were removed. Two more instillations of SK-SD at other sites resulted in the removal of 600 cc. more. Three more enzyme injections were made, but each time subsequent taps yielded only from 2 to 10 cc. No change was observed in the roentgenograms.

Case 3 (26). A 37-year-old man was struck by small-arms fire in the left leg on 7 August 1950 in Korea. He sustained a compound, comminuted fracture of the middle third of his left tibia. His leg was placed in a cast and he was transferred to this hospital. On arrival the cast was removed, revealing a soft tissue defect 6 by 8 cm. through which a small piece of the tibia protruded. A long leg cast, windowed over the affected area, was applied. Two small sequestrums were removed 5 days later on 27 August. There was seropurulent drainage, cultures of which showed mixed flora. Despite antibiotic therapy and other measures, the area on 6 September appeared as shown in figure 3 and, because of soft tissue infection and osteomyelitis, SK-SD was used in the form of wet soaks until 2 October, when the leg showed remarkable improvement (fig. 4).

(26) This case was reported by Spittler, A. W.; Hakala, E. W.; and Midgley, E. W.: Enzymatic débridement of war wounds. M. Ann. District of Columbia. In press.

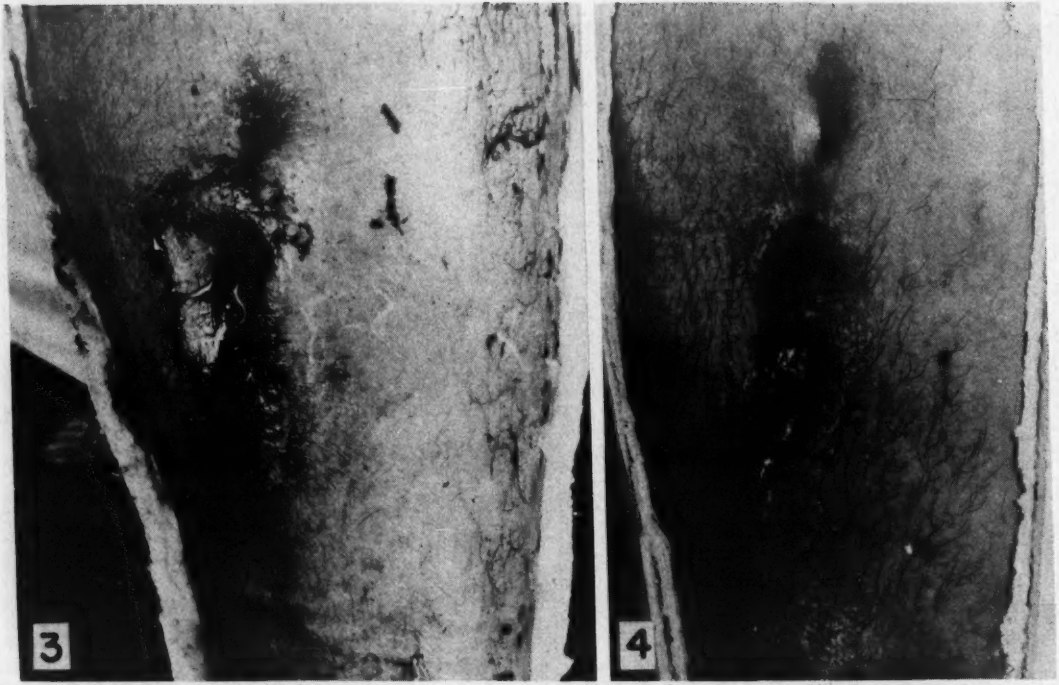

Figure 3 (case 3). Photograph of left leg taken 6 September 1950 on which day enzymatic débridement was begun with SK-SD.
Figure 4 (case 3). Photograph taken 2 October 1950 when therapy was completed.

Figure 5 (case 4). Photograph of amputation stump, left thigh, taken 2 March 1951, the day trypsin therapy was begun.

Figure 6 (case 4). Photograph taken 8 April 1951 at the completion of tryptic débridement.

Case 4. A 22-year-old man was struck in the left upper thigh by an automatic rifle bullet in Korea on 3 February 1951. He sustained a severed femoral artery and a compound, comminuted fracture of the upper third of his femur. An open amputation above the left knee was performed on 6 February. Antibiotics, blood, and plasma were given. The patient was admitted to this hospital on 19 February where examination disclosed foul drainage and much necrotic tissue on the stump. No improvement was noted on conventional treatment and trypsin therapy in the form of wet soaks and dry dusting powder was given from 2 March to 8 April (figs. 5 and 6). It was estimated that the healing time was shortened 3 months by the use of trypsin.

SUMMARY

The use of enzymes in débridement has been chiefly effective against clotted blood, thick pus, or necrotic material as found in a variety of clinical conditions. Systemic reactions have been noted only in the intrapleural use of these enzymes. No reaction, except occasional burning with trypsin, have been reported on their local use. SK and SD are antigenic, and perhaps some failures in treatment may be explained on this basis as in the case of a patient who has had repeated streptococcal infections and has developed antistreptokinases and antistreptodornases.

Our results in this hospital with local application paralleled those of other investigators, but the results in a series of 9 patients with chest conditions have not been as satisfactory as the reports of others had led us to expect. This may be due to the fact that nearly all of our patients had conditions of too long duration.

Concurrently with enzymatic therapy, appropriate antibacterial, nutritional, and supportive measures must be taken. By dissolving fibrin and nucleoprotein in which bacteria are trapped, the enzymes allow antibiotics and macrophages easier access to the bacteria and in this way help to "sterilize" the area. The enzymes in themselves are not bactericidal or bacteriostatic. When viewed in its proper perspective, enzymatic débridement is a valuable accessory tool in both medical and surgical management.

The Influence of p-(di-n-propylsulfamyl)-Benzoic Acid on the Excretion of Uric Acid[1]

Forrest W. Pitts, *Captain, MC, U. S. A.*

John S. Chambers, *M. S.*

BENEMID (p-(di-n-propylsulfamyl)-benzoic acid) *(2)* is capable of influencing the urinary excretion of certain substances which are excreted via the renal tubular mechanism. Specifically, it is capable of enhancing plasma concentrations of both penicillin and para-aminosalicylic acid (PAS) by modifying the urinary excretion of these substances *(3)*. Carinamide is also capable of delaying the excretion of penicillin and PAS by altering renal tubular function *(4, 5)*. Carinamide may increase the urinary excretion of uric acid by inhibiting the reabsorption of uric acid from the glomerular filtrate and thus decrease the serum uric acid concentration *(6)*. Because benemid is similar chemically and in pharmacologic action to carinamide, an investigation was carried out on 7 subjects to determine its uricosuric effect as compared to that of the known uricosuric agent, aspirin.

METHOD

Seven men whose sole reason for hospitalization was pulmonary tuberculosis were selected for this study. Preliminary evaluation for renal abnormalities included urinalysis, 15-minute phenolsulfonphthalein

(1) Research and Development Branch, Fitzsimons Army Hospital, Denver, Colo.

(2) Supplied through the courtesy of Sharpe and Dohme, Inc.

(3) Boger, W. P.; Beatty, J. O.; Pitts, F. W.; and Flippin, H. F.: Influence of new benzoic acid derivative on metabolism of para-aminosalicylic acid (PAS) and penicillin. Ann. Int. Med. 33: 18-31, July 1950.

(4) Boger, W. P.; Pitts, F. W.; and Gallagher, M. E.: Benemid and carinamide; comparison of effect on para-aminosalicylic acid (PAS) plasma concentrations. J. Lab. & Clin. Med. 36: 276-282, Aug. 1950.

(5) Boger, W. P., and Flippin, H. F.: Penicillin plasma concentrations; increase and prolongation with carinamide and newer depot penicillin preparations. J. A. M. A. 139: 1131-1136, Apr. 23, 1949.

(6) Wolfson, W. Q.; Cohn, C.; Levine, R.; and Huddlestun, B.: Transport and excretion of uric acid in man; physiologic significance of uricosuric effect of carinamide. (Abstract) Am. J. Med. 4: 774, May 1948.

excretion, Fishberg concentration test, and urea clearance. None gave a history of antecedent renal disease and objective evaluation of the renal status was normal by the above criteria. During the course of this study all subjects received a diet containing 2,500 calories with 100 grams of protein daily. Exogenous purine intake was controlled but not restricted.

The study was initiated by obtaining fasting blood uric acid levels on all subjects and coincidentally collecting 24-hour urine specimens for quantitative uric acid determinations. The subjects then received 0.5 gram of benemid orally every 6 hours for 5 days. On the fifth day a fasting blood uric acid determination was made and a 24-hour urine specimen collected for a quantitative determination of uric acid. After

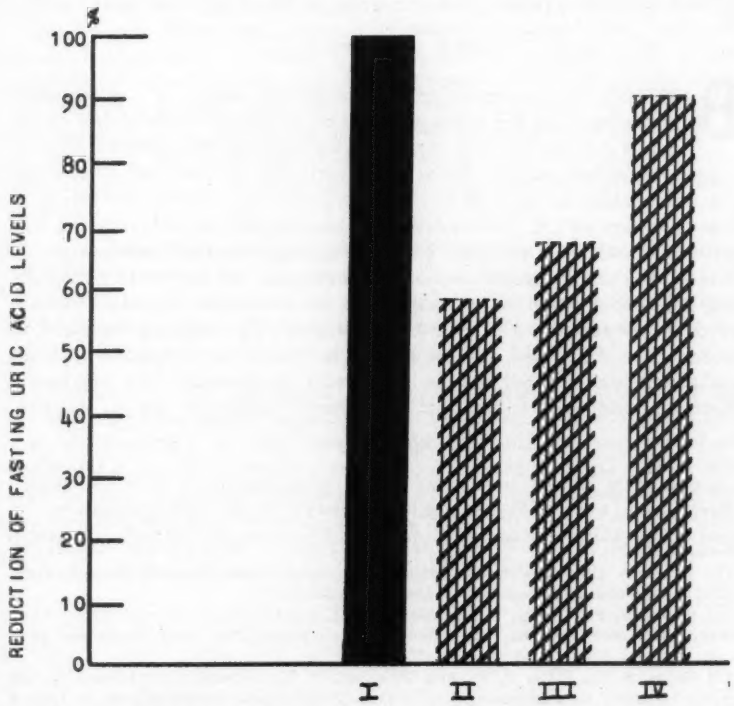

Figure 1. The influence of benemid and aspirin on fasting blood uric acid determinations (averages of 49 determinations from the same 7 patients).

I = Control (average of 3 determinations on each patient).
II = 0.5 gram of benemid every 6 hours (average of 2 determinations on each patient).
III = 1 gram of aspirin every 6 hours.
IV = 0.5 gram of benemid and 1 gram of aspirin concurrently every 6 hours.

1 week, the control study was repeated and again followed by the administration of 0.5 gram of benemid every 6 hours for 5 days. Blood and urine samples were collected in an identical manner. One week later the subjects received 1 gram of aspirin every 6 hours for 5 days. On the fifth day the fasting blood uric acid level was determined and coincidentally a 24-hour urine specimen was collected to determine the amount of uric acid excreted. The control evaluation was repeated 1 week later. This was followed by the concomitant administration of 0.5 gram of benemid and 1 gram of aspirin every 6 hours for 5 days when fasting blood specimens were again obtained. All uric acid determinations were performed by the method of Folin and correction was not made for nonurate chromogens (7, 8).

TABLE 1. *The influence of benemid and aspirin on fasting blood uric acid levels (mg. per 100 cc.)*

Subject	Control	Benemid		Aspirin		Benemid and Aspirin	
	(1)	(2)	(3)	(4)	(3)	(5)	(3)
1	3.17	1.71	-46	1.86	-41	3.14	-1
2	3.07	1.68	-45	1.42	-54	3.14	+2
3	3.20	1.65	-48	1.40	-56	2.76	-14
4	2.43	2.03	-16	3.01	+24	3.90	+60
5	2.96	1.67	-44	2.41	-19	3.20	+8
6	2.60	1.38	-47	1.78	-32	2.80	+8
7	2.42	1.47	-39	1.56	-36	2.90	+20
Average	2.84	1.66	-42	1.92	-33	3.12	+10

(1) Average of 3 determinations.
(2) Average of 2 determinations following dose of 0.5 gram every 6 hours for 5 days.
(3) Percent change relative to control determination.
(4) Following dose of 1 gram every 6 hours for 5 days.
(5) Following dose of 0.5 gram of benemid and 1 gram of aspirin every 6 hours concurrently for 5 days.

RESULTS

Without exception the administration of benemid was accompanied by a decrease in fasting blood uric acid levels as compared to the control determinations. The decrease varied from 16 to 48 (average 42) percent. Aspirin in doses of 1 gram every 6 hours produced a decrease in fasting blood uric acid levels varying from 19 to 56 (average 33) percent. One subject did not show a decrease in fasting blood uric

(7) Folin, O.: Improved method for determination of uric acid in blood. J. Biol. Chem. 86: 179-187, Mar. 1930.

(8) Robinson, W. D., and Block, W. D.: Effect of salicylates on blood concentration and urinary excretion of urates and non-urate chromogens. Proc. Central Soc. Clin. Research 19: 69, 1946.

acid or associated uricosuric effect following the administration of aspirin but did respond to benemid. The fact that the combination of aspirin and benemid did not significantly alter the fasting blood uric acid levels was surprising. The effect of benemid and aspirin administered singly and in combination on fasting blood uric acid levels in these patients is shown in figure 1 and table 1.

Coincident with the decrease in serum uric acid levels produced by benemid and aspirin, an increase in the 24-hour urinary uric acid excretion was observed (table 2). Subjects who received benemid manifested an increase in urinary uric acid excretion varying from 47 to 100 (average 71) percent. Similarly, aspirin produced an increase in urinary uric acid excretion ranging from 21 to 100 (average 50) percent as compared to the control determinations.

TABLE 2. *The influence of benemid and aspirin on urinary uric acid excretion (mg. per 24 hours)*

Subject	Control	Benemid		Aspirin	
	(1)	(2)	(3)	(4)	(3)
1	573	841	+47	693	+21
2	346	656	+90	645	+86
3	470	722	+54	942	+100
4	632	1080	+71	316	-50
5	497	993	+100	976	+96
6	344	575	+67	671	+95
7	391	701	+79	637	+63
Average	465	795	+71	697	+50

(1) Average of 3 determinations.
(2) Average of 2 determinations following dose of 0.5 gram every 6 hours for 5 days.
(3) Percent change relative to control determinations.
(4) Following dose of 1 gram every 6 hours for 5 days.

DISCUSSION

Uric acid is excreted predominantly in the urine and only traces of uric acid are found in intestinal secretions. Practically all of the urates in the plasma are in a filtrable form and, therefore, the quantity of urate filtered is a function of the filtration rate and plasma urate concentration. Normally from 5 to 6 mg. of urate is filtered each minute, but, because of the tubular reabsorption, less than 10 percent of this quantity is excreted in the urine. Conditions producing or accompanying acidosis, such as starvation, a high fat diet, exercise, or injections of lactic acid, diminish uric acid excretion. On the other hand, mercurial diuretics, aminophylline, salicylates, glucose, phenol red, and diodrast will promote urinary uric acid excretion *(9)*.

(9) Duncan, G. G. (editor): Disease of Metabolism: Detailed Methods of Diagnosis and Treatment. W. B. Saunders Co., Philadelphia, Pa., 1947. p. 619.

Benemid is capable of inhibiting the conjugation of glycine with less PAS which normally occurs in both the liver and the kidney *(10)*. This had led to the assumption that the conjugated form of PAS is more readily excreted by the renal tubular mechanism than is its free form. The mode of action of benemid in delaying the excretion of such substances as penicillin, diodrast, phenolsulfonphthalein and para-aminohippuric acid, however, is believed to be by inhibition of renal tubular mechanisms *(11)*. Such a mode of action might be applied to the uricosuric properties of benemid by assuming that this agent interferes with tubular reabsorption of uric acid from the glomerular filtrate. Benemid, like carinamide, produces a diminution in urinary 17-ketosteroids *(12, 13)* which may be the common denominator for the varied pharmacologic effects of benemid.

When it was demonstrated that carinamide would increase urinary excretion of uric acid, an investigation of benemid, which is chemically and pharmacologically similar to carinamide, was suggested. Benemid is superior to carinamide in that its duration of action is longer and it may be administered in smaller doses (0.5 gram benemid every 6 hours as compared to 3 grams of carinamide every 3 hours). The advantage of benemid over relatively larger doses of salicylates is shown by the fact that the former agent possesses equal or superior uricosuric properties associated with the practical ease of administration. No toxicity has been noted when benemid is administered in doses of 2 grams over protracted periods of time *(14)*. Because aspirin antagonizes the uricosuric action of benemid, the concomitant use of the latter agent is contraindicated.

The cause of gout and its relationship to abnormal uricosuric acid metabolism is still poorly understood. Recent investigation in patients with early stages of gout *(15)*, as well as isotope studies determining the total miscible uric acid pool in patients with chronic gout *(16)*, suggest that the crux of the metabolic error is attributable to over-

(10) Boyer, K. H.; Wiebelhaus, V. D.; Tillson, E. K.; Russo, H. F.; and Wilhoyte, K. M.: Benemid (p-(di-n-propylsulfamyl) benzoic acid); inhibition of glycine conjugative reactions. Proc. Soc. Exper. Biol. & Med. 74: 772-775, Aug. 1950.

(11) Boger, W. P.; Matteucci, W. V.; Schimmel, N. H.; and Flippin, H. F.: Benemid; Its influence on PAS, penicillin, and other antibiotics. Scientific Exhibit presented at The Atlantic City Session of the American Medical Association. June 11-15, 1951.

(12) Bissell, G. W.; Longstreth, H. P.; and Gilbert, F. M.: Inhibition of urinary excretion of 17-ketosteriods by caronamide. Proc. Soc. Exper. Biol. & Med. 72: 584-585, Dec. 1949.

(13) Gardner, L. I.; Crigler, J. F.; and Migeon, C. J.: Inhibition of urinary 17-ketosteriod excretion produce by "Benemid." Proc. Soc. Exper. Biol. & Med. 78: 460-463, Nov. 1951.

(14) Boger, W. P., and Strickland, S. C.: Benemid; preliminary assessment of its toxicity in man. Tenth Conference on Chemotherapy of Tuberculosis (VA). Jan. 1951. pp. 292-298.

(15) Friedman, M., and Byers, S. O.: Increased renal excretion of urate in young patients with gout. Am. J. Med. 9: 31-34, July 1950.

(16) Benedict, J. D.; Forsham, P. H.; and Stetten, DeW., Jr. Metabolism of uric acid in normal and gouty human studied with aid of isotopic uric acid. J. Biol. Chem. 181: 183-193, Nov. 1949.

production of endogenous uric acid rather than underexcretion of uric acid. Recent work has demonstrated that benemid is capable of acting as a uricosuric agent in patients with gout *(17)*. Although it does not influence or modify acute arthritic exacerbations of gout, the application of a uricosuric agent such as benemid to prevent or minimize irreversible joint or renal damage is logical and merits continued study.

SUMMARY

Fasting blood uric acid determinations and 24-hour urinary uric acid determinations were performed in 7 subjects with normal renal function. Dietary exogenous uric acid intake was controlled but not restricted. Benemid produced an average of 42 percent decrease in the fasting uric acid level and concomitantly the average 24-hour urinary excretion of uric acid was increased by 72 percent. Aspirin produced an average of 33 percent decrease in the fasting blood uric acid level with an average of 50 percent increase in the 24-hour urinary uric acid excretion. Aspirin antagonized the uricosuric action of benemid.

(17) Gutman, A. B.: Some recent advances in study of uric acid metabolism and gout. Bull. New York Acad. Med. 27: 144-164, Mar. 1951.

BOOK REVIEW

Psychotherapy of Psychosis, by *Gustav Bychowski,* M. D., Assistant Clinical Professor of Psychiatry, New York University College of Medicine. 328 pages. Grune & Stratton, New York, N. Y., publisher, 1952. Price $5.75.

Despite its title very little of this book is devoted to therapy. Most of it deals with such topics as theories of schizophrenia, phenomenology, and the psychology of elation. The total effect is that of an inadequate, poorly organized effort to cover the field of psychiatry. Although many psychiatrists would agree with statements made and positions taken by the author, it is difficult to know for whom the book can be recommended. There is not sufficient clarity, simplicity, and detail for it to be useful to the new trainee and certainly not sufficient depth to recommend it to the advanced student. A paragraph quoted from the chapter entitled "Problems of Transference" is fairly typical:

"You will remember that we have discussed at some length the handling of hostility and the negative transference. We now have to emphasize once more that allowing the hidden hostility of the patient to accumulate may be one of the greatest handicaps of therapy. Accordingly, we have to detect the negative attitude and to approach it with tact, courage, and, as far as possible, without fear and hostility. We also must proceed at times with great caution and passivity in order to avoid the provocation of hostility which, in a schizophrenic, may lead to negativism, stupor, catatonic, excitement, etc."

—*Commander M. E. Roudebush, MC, U. S. N.*

Prevention of Skin Damage by Sunlight[1]

Charles D. Bell, *Captain, MC, U. S. N.* (2)

Walter F. Mazzone, *Lieutenant, MSC, U. S. N. R.* (2)

IT is the purpose of this article to point out the damage to the skin produced by repeated overexposure to sunlight, the mechanism by which the noxious effects are inflicted, and a practical method of prevention. Such a discussion is particularly appropriate for naval personnel because of their occupational overexposure, by reason of which the primary changes in the skin are so characteristic that the condition is known as "sailors skin." At the risk of increasing the number of synonyms, the term "heliodermatosis" is proposed as being more apt than the preceding title.

Clinically, heliodermatosis is seen in the habitually uncovered areas of the body. It is manifested early by a peculiar mottled bluish whiteness, best discerned on the lower lids, the cheeks, and the backs of the hands, this background being etched by tiny, dilated blood vessels. As exposure continues the telangiectases multiply, accompanied by atrophy and consequent accentuation of the follicular orifices, giving a grossly florid and pebble-grained appearance. The skin of all the affected areas becomes thin, lax, and without luster, except on the back of the neck where it is markedly thickened. Here the wrinkles deepen into furrows and thereby produce a rugose surface. Eventually small scaling patches appear which in time become indurated papules, darker perhaps than the surrounding skin, due to oxidation of the heavy keratin layer. Not infrequently the lower lip is involved too, being dry, scaly, sometimes fissured, and sometimes exhibiting leukoplakia. The papules are senile keratoses, to which the condition of the lip is analogous, and both have the potentiality of becoming prickle-cell epitheliomas. A papule or nodule of a different character, exhibiting a raised border and usually a crusted or frankly ulcerated center, may also be present.

(1) Preliminary investigation was conducted in 1948 at the U. S. Naval Hospital, St. Albans, N. Y.

(2) U. S. Naval Hospital, San Diego, Calif.

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This is a basal-cell epithelioma. Those persons prone to sunburn, especially those who blister, are most readily affected and among these, the most susceptible are the red-haired, freckled types (3). Because the permanent changes produced by a single sunburn are small, heliodermatosis develops by cumulation, and therefore is usually seen after the age of 50.

Histologically, heliodermatosis is characterized by a relative hyperkeratosis with follicular plugging. Atrophy of the epidermis varies from simple loss of the rete pegs to actual thinning of the Malpighian layer. Most prominent in the subpapillary zone, but also sometimes found in the mid-zone of the corium, are collagen fibers which have lost their normal affinity for eosin, take the blue stain of hematoxylin, and are said to have undergone "basophilic degeneration" (4). The affected fibers may be coarsened by this change, or homogenized into an amorphous mass. Usually there is a nonspecific inflammatory infiltrate of lymphocytes. The superficial vessels of the corium are dilated and congested (telangiectases), but the adnexal elements are not involved.

Heliodermatosis is found only in skin that has been subjected to habitual sunburn and frequently the patient is found to have an outdoor occupation. Almost invariably it is associated with keratosis senilis and often it heralds the occurrence of an epithelioma. Although skin cancer occasionally appears on the covered portions of the body, an incidence of about 90 percent on the habitually exposed skin reveals how strongly sunlight can be incriminated. The usual sequence of events is heliodermatosis of varying degree, keratosis senilis, leukoplakia of the lower lip, and, finally, epithelioma of the skin and lip.

Hall (5) found that the predisposing factors for sunlight are not hair coloring, as is frequently stated, but rather racial stock and eye color. He concluded that sunlight was the pre-eminent carcinogen for those of Scotch-Irish-English ancestry, North Europeans, and possibly all homozygous blue-eyed persons. Blum (6) stated that sunlight is an important causative factor in skin cancer. Dorn (7) found that cancer of the skin and lip was much more prevalent in the southern United States, where there is more sunlight, than in either the North or the West, not only for the white population, but also for the Negro. Peller (8) found that 50 percent of the patients with skin and lip cancer in the Armed

(3) Belisario, J. C.: Cutaneous cancer and precancer. Brit. J. Dermat. 61: 295, Aug.-Sept. 1949.

(4) Percival, G. H.; Hannay, P. W.; and Duthie, D. A.: Fibrous changes in dermis with special reference to senile elastosis. Brit. J. Dermat. 61: 269-276, Aug.-Sept. 1949.

(5) Hall, A. F.: Relationship of sunlight, complexion and heredity to skin carcinogenesis. Arch. Dermat. & Syph. 61: 589-610, Apr. 1950.

(6) Blum, H. F.: Radiation: Photophysiologic and pathologic process. In Glasser, O. (editor): Medical Physics. Year Book Publishers, Inc., Chicago, Ill., 1944. vol. 1, pp. 1145-1157.

(7) Dorn, H. F.: Illness from cancer in United States. Pub. Health Rep. 59: 33-45, Jan. 14, 1944; 65-77, Jan. 21, 1944; 97-114, Jan. 28, 1944.

(8) Peller, S.: Epidemiology of skin cancer. J. Invest. Dermat. 11: 73-80, July 1948.

Forces were born in the South but that only 27 percent were from the North. On comparing the incidence in service personnel born in the North with that found by Dorn for the northern civilian population, he discovered it to be almost twice as high, emphasizing the effect of occupational exposure.

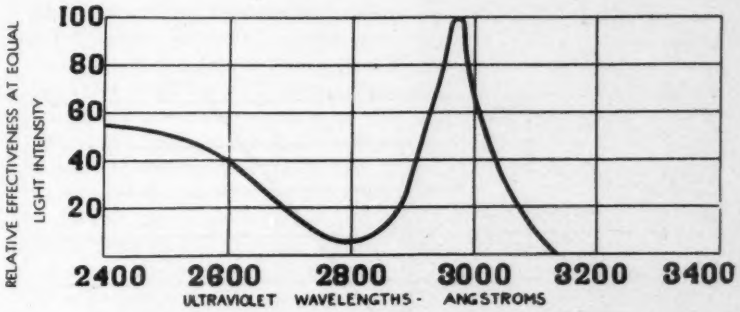

Figure 1. Erythema production. (Reproduced by permission of the Hanovia Chemical and Manufacturing Company, Newark, N. J.)

The electromagnetic spectrum of sunlight extends from about 2,400 to 12,000 angstroms. Ultraviolet light is contained in the range between 2,400 and 4,000 angstroms. Figure 1 shows erythema production by the various wave lengths of the ultraviolet band. Ultraviolet light of the quality of 2,537 angstroms is capable of producing a moderate erythema, which is different from true sunburn in that it occurs after a latent period of about 15 minutes, fades comparatively quickly, and is not followed by blistering or desquamation (2). This is the type of radiation emitted by the cold-quartz lamp. Ultraviolet light of 2,970 angstroms produces the greatest erythema, the most pronounced physiologic effects, and true sunburn. This erythema appears only after a latent period of several hours and, if in a great enough dose, is followed by blistering, desquamation, and red-brown pigmentation. This is the type of radiation emitted by the mercury-vapor lamp and by the Kromayer lamp. Ultraviolet light of the quality of 3,130 angstroms is responsible for the darkening of already-formed, red-brown melanin but produces no other effects (9). This radiation is the so-called "near" ultraviolet. Figure 2 shows transmission of ultraviolet light through 1 mm. of human skin. Near ultraviolet radiation has the greatest ability to penetrate, but produces no damaging effects. The actinic band of sunlight, 2,970 angstroms, has excellent penetrating power, but the 2,537-angstrom band has almost no ability to penetrate, despite its power to produce erythema. From these facts it is evident that protection against the 2,970-angstrom band of ultraviolet light would prohibit the

(9) Blum, H. F., and Terus, W. S.: Inhibition of erythema of sunburn by large doses of ultraviolet radiation. Am. J. Physiol. 146: 97-106, Apr. 1946.

sequelas of sunburn. Blum and Kirby-Smith *(10)* have shown that physiologic protection depends on a thickened stratum corneum, and not on pigmentation, as is often supposed. For example, although the palms and soles have little or no pigment, even in the colored races, they have the heaviest keratin layer and are the most resistant to sunburn of all skin areas.

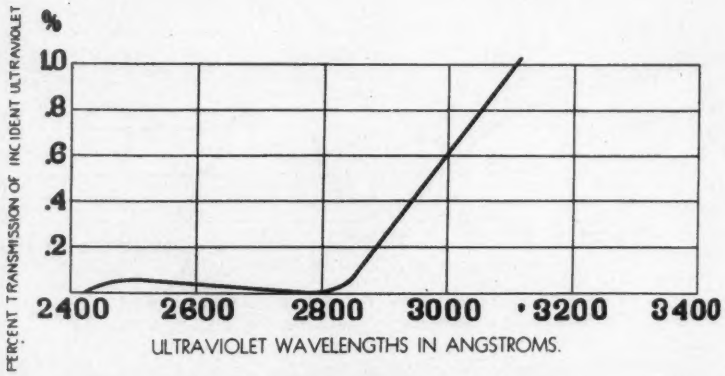

Figure 2. Transmission of ultraviolet light through 1 mm. of live human tissue. (Reproduced by permission of the Hanovia Chemical and Manufacturing Company, Newark, N. J.)

The following is a condensation of the physical aspects of light radiation *(11)*. The intensity of ultraviolet light reaching the earth's surface is directly dependent on the thickness of the atmosphere. Because less atmosphere is traversed by the rays when the sun is at its zenith than when it is rising or setting, intensity is greatest at noon. For the same reason, and because of the earth's inclination, latitude and season also cause variation in intensity. Absorption by the atmosphere varies with the wave length, ultraviolet being absorbed to a greater extent than visible light. Ozone is the best absorber, being present in greatest quantity over the poles. It is reduced in amount during the summer. Smoke, too, is an excellent absorber and an amount barely perceptible to the eye may screen ultraviolet light completely. Water and dust scatter the radiation instead of absorbing it and much of the sunburn spectrum reaching the earth's surface is scatter or "sky" radiation. For this reason severe sunburns may be sustained on hazy, cloudy, or foggy days because of underestimation of exposure and because of the bending of the rays into supposedly shaded areas. Snow, water, and ice reflect ultraviolet light, thereby increasing the dosage of a given exposure and resulting in so-called snow burn or glacier burn. Green foliage and soil are absorbers. All factors considered then, sun-

(10) Blum, H. F., and Kirby-Smith, J. S.: Natural protection against sunburn. Science 96: 203-204, Aug. 28, 1942.

(11) Blum, H. F.: Military aspects of sunburn. War Med. 4: 388-399, Oct. 1943.

burn expectancy would be greatest on a snow-capped peak, near the equator, at noon on a clear day, at the time of the equinox.

Artificial protection against sunburn is provided by many available commercial preparations, but because of popular demand for tanning, few of them screen completely against the actinic band of ultraviolet light. An ointment containing 2 percent each of tannic acid and salol is such a sun filter. Homomethyl salicylate and menthyl anthranilate are nearly complete screening agents, but both are rare chemicals, difficult to obtain, and the former has a peculiar odor which might make it objectionable. Rothman *(12)* noted that procaine hydrochloride injected intradermally prevented tanning of the wheal site of an area exposed to ultraviolet light though it did not prevent the initial erythema. It was then shown spectroscopically that procaine screened out the actinic band, but did not absorb the 2,537-angstrom band. Later he and Rubin *(13)* showed that para-aminobenzoic acid (PABA) was the fraction of procaine responsible for this effect. Spectroscopically PABA totally absorbs the ultraviolet light between 2,600 and 3,130 angstroms. Because it has no action below 2,600 angstroms, it will not prevent initial erythema and because light above 3,130 angstroms is free to act, it will not prevent darkening of pigment already present. Hence it will not protect against freckling. They recommended an ointment containing from 10 to 15 percent of PABA as extremely effective against sunburn.

Because this appeared to be the most readily available agent the problem was posed of providing it for naval personnel in a preparation which would not be distasteful because of altered appearance, odor, or tactile sense. PABA in Ruggles' cream, as recommended by Rothman and Rubin, met most of the requirements, but like all ointments, it is not readily acceptable to men. Furthermore Ruggles' cream is a difficult recipe to compound, even by an expert pharmacist, and contains ingredients not available in the Armed Services Catalog of Medical Materiel. PABA is not easily adaptable to common ointment bases because of its insolubility. The sodium salt of PABA *(14)*, however, is readily soluble both in alcohol and water, thus solving that part of the problem and obviating the necessity for an ointment.

By exposing subjects to erythema doses of ultraviolet light, having small areas protected with NaPABA, homomethyl salicylate, menthyl anthranilate, and tannic acid and salol, it was determined that NaPABA gave protection superior to that provided by the other agents. Figure 3 shows the results. By exposing subjects partially protected by different percentages of NaPABA in different combinations of alcohol and water to the therapeutic lamp, it was determined that 5 percent NaPABA in

(12) Rothman, S.: Reduction of inflammation and pigmentation from light by injections of novocain. Strahlentherapie 22: 729-735, 1926.

(13) Rothman, S., and Rubin, J.: Sunburn and para-aminobenzoic acid. J. Invest. Dermat. 5: 445-457, Dec. 1942.

(14) Suggested and supplied through the courtesy of Louis Freedman, Ph. D., U. S. Vitamin Corporation, New York, N. Y. Dr. Paul R. Kline, civilian consultant, U. S. Naval Hospital, St. Albans, N. Y., gave valuable advice.

equal parts of alcohol and water gave the maximum protection. Tween 80 was added to the formula to permit easy spreading, even on naturally oily skin, and to insure penetration into wrinkles and follicles, making certain of an unbroken film over the selected area. The following lotion to be applied prior to exposure is recommended:

	Grams or cc.
NaPABA	5.
Tween 80	2.
Water and alcohol in equal parts to make	100.

It dries quickly, leaving no telltale evidence of its presence. It causes a tan discoloration of cotton or woolen clothing, removable by cleaning, but may permanently discolor rayon or nylon. Being water-soluble, it loses its protective ability after about 3 hours of average sweating.

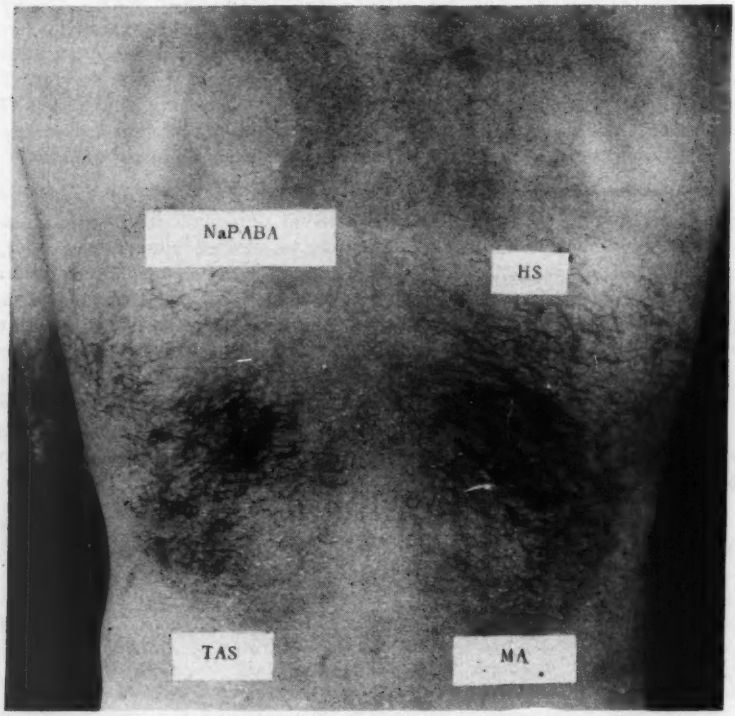

Figure 3. Photograph comparing effect of ultraviolet light on 4 treated areas.

NaPABA - Sodium PABA
HS - Homomethyl salicylate
TAS - Tannic acid and salol
MA - Menthyl anthranilate

Just as men prefer a liquid preparation, women readily accept a nongreasy ointment because it can be employed as a cosmetic base. Ointment base, water-soluble (item 1-316-420 of the Armed Services Catalog of Medical Materiel) is an excellent vanishing cream which serves admirably as a vehicle for NaPABA. The following ointment to be applied prior to exposure is recommended:

	Grams or cc.
NaPABA	5.
Cetyl alcohol	15.
Cera alba	1.
Propylene glycol . . .	10.
Sodium lauryl sulfate .	2.
Water	72.

No perfume should be added to either the lotion or the ointment because of the photosensitizing effect of oil of bergamot, present in most perfumes and colognes.

Having developed elegant and efficient preparations for service personnel and their dependents, the stumbling block of nonavailability of NaPABA in the Armed Services Catalog of Medical Materiel remained. Consequently its use was limited to those stations having adequate open purchase funds. PABA, however, is available in U. S. P. reagent grade as Item 1-059-400. One of us (WFM) was able to develop a simple process for converting this to the sodium salt by treating sodium bicarbonate with PABA. By comparison of molecular weights, it became evident that 18.4 grams of sodium bicarbonate were required to neutralize or convert 30 grams of PABA. The above weights, mixed together, are dissolved in 100 cc. of distilled water. When this solution stops effervescing, it is placed on a water bath and evaporated just to the point of crystallization. It is then cooled to room temperature and placed in the refrigerator to complete the process of crystallization. If the original solution is heated to dryness on the water bath, the crystals so formed are unduly hard and difficult to powder. Crystallization being complete, the solution is filtered, the crystals are air-dried, powdered, and are then ready for use. Solutions of NaPABA prepared from these crystals exhibit a weakly alkaline reaction and have a sodium content of 12.1 percent.

In 3 years' use of NaPABA on several hundred patients, only 1 developed an allergic eczematous contact-type of dermatitis from this agent. Baer *(15)* has emphasized the relationship of cross sensitivity between PABA and related compounds such as sulfonamides, picric acid, paraphenylene diamine, azo dyes, and the various topical anesthetics related to procaine (benzocaine, pontocaine, tetracaine, et

(15) Baer, R. L.: Examples of cross sensitization in allergic eczematous dermatitis. Arch. Dermat. & Syph. 58: 276-285, Sept. 1948.

cetera). He defined this phenomenon as a sensitization not only to the primary allergen, but also to one or more immunochemically related secondary allergens. It is apparent from the foregoing list that persons constantly are exposed to one or more of these allergens and therefore the possibility of an allergic eczematous contact-type of dermatitis on exposure to NaPABA should be borne in mind. In the light of our experience, the probability of such an occurrence is considered to be remote.

SUMMARY

Heliodermatosis and skin cancer result from repeated overexposure to sunlight, an occupational hazard of naval personnel. Because of a lack of physiologic protection, the most susceptible persons are those of Scotch-Irish-English ancestry and, perhaps, all homozygous blue-eyed persons. The actinic band of sunlight, around 3,000 angstroms, is responsible for the permanent changes induced in the skin. NaPABA is markedly effective in screening out this band of the sunlight spectrum. It is readily available to naval personnel and easily incorporated in standard pharmaceutical preparations.

BOOK REVIEW

Histopathological Technic, Including a Discussion of Botanical Microtechnic, by *Aram A. Krajian,* Sc. D., Formerly in Department of Pathology, Los Angeles County General Hospital, Los Angeles, Calif., and *R. B. H. Gradwohl,* M. D., Pathologist to Christian Hospital; Director, Gradwohl School of Laboratory and X-Ray Technique, St. Louis, Mo. 2d edition. 362 pages; 131 text illustrations and 7 color plates. The C. V. Mosby Company, St. Louis, Mo., publisher, 1952. Price $6.75.

The authors have made available again a useful compilation of methods used in tissue diagnosis. Twelve years have elapsed since the appearance of the first edition. In addition to the easily understood presentation of all the commonly used methods for fixing, embedding, staining, botanical microtechnic, and miscellaneous procedures, such as preparation of museum specimens, the new edition includes methods using the technicon tissue processor, preparation of smears for cytologic study, and a section on the care and use of microtome knives. The discussion and interpretation of smears is rather lengthy for a book on technical methods, and might better be left to publications devoted to the smear technic. A presentation of tissue processing and staining methods using the technicon with not only the technicon solutions and stains but also conventional fluids and stains would have been a valuable addition to the book. The tissue technician will find the book a handy source for a variety of tried and proved methods, and the pathologist will find the sections on special stains especially useful.—*Commander C. M. McCandless, Jr., MC, U. S. N.*

Bronchiectasis as a Source of Massive Pulmonary Hemorrhage

Robert T. Gants, *Colonel, MC, U. S. A.*

James M. Cuthbertson, *Captain, MC, A. U. S.*

MASSIVE bleeding may arise as a complication of several diseases of the chest, such as pulmonary tuberculosis, bronchial carcinoma, aneurysm of a pulmonary vessel, pulmonary arteriovenous fistula, lung abscess, and foreign body in a bronchus. Bronchiectasis has been implicated rarely as a source of massive hemorrhage. In most patients (except those with aneurysm of a pulmonary vessel) massive pulmonary hemorrhage is preceded by cough, slight to moderate hemoptysis, fever, weight loss, and pain. The common presenting complaint of persons with bronchiectasis is chronic cough with expectoration of large quantities of purulent sputum which is sometimes streaked with blood. There may be recurring bouts of mild to moderate hemoptysis. Hawkins and Clagett *(1)* called attention to the fact that massive pulmonary hemoptysis may be a primary symptom of bronchiectasis as is illustrated in their report of 2 patients, 1 of whom had pulmonary hemorrhage as the main complaint, there being an antecedent history of a dry cough and low grade fever. The other patient had fever and a cough productive of excessive amounts of foul sputum in addition to episodes of massive bleeding. Our case is presented to point out the fact that massive pulmonary hemorrhage may be the first and only symptom in a patient with an apparently mild case of bronchiectasis.

CASE REPORT

A white soldier, age 33 years, presented himself to a U. S. Army Hospital in Germany on 13 February 1951 because he had allegedly coughed up a pint of bright red blood. While in the admission office

(1) Hawkins, W. D., and Clagett, O. T.: Massive hemoptysis as primary symptom of bronchiectasis; report of 2 cases. Proc. Staff Meet., Mayo Clin. 20: 337-340, Sept. 19, 1945.

he suddenly coughed up 250 cc. of bright red frothy blood. He had enjoyed excellent health until 2 weeks before, when he developed a dry cough which he attributed to excessive smoking. There was no history of weight loss, fatigue, fever, or night sweats. His past history was insignificant except that at the age of 16 years he had suffered an illness characterized by cough, pain in the left side of the chest, fever, and mild hemoptysis, from which he recovered after 1 week.

Physical examination was negative except for findings characteristic of blood loss and the presence of clubbing of all fingers which had been present for about 1 year. An anteroposterior roentgenogram of his chest was negative. His hemoglobin was 10.9 grams with a hematocrit of 34.5. His white blood cell count was normal.

During his stay in that hospital his temperature ranged from 100° to 105° F. each day. Studies to determine the cause of the hemorrhage included sputum culture and examination of his gastrointestinal tract, nasopharynx, and accessory sinuses. Because he was a heavy drinker, hepatic cirrhosis with esophageal varicosities or the aspiration of vomitus followed by pulmonary abscess were considered. He was given whole blood transfusions and penicillin. One week after admission he suffered another pulmonary hemorrhage, losing 1,900 cc. of bright red, frothy blood. His hemoglobin level dropped to 8.9 grams. He was given whole blood transfusions and transferred to a general hospital where a roentgenogram of the chest revealed a slight elevation of the left diaphragm with a rounded area of increased density in the lower lobe of his left lung overlying the apical portion of the cardiac shadow (fig. 1). Bronchoscopy revealed old blood clots in the left main stem bronchus. A later bronchoscopic examination, followed by bronchograms, confirmed the fact that the bleeding was from the bronchus of the lower lobe of the left lung in which there were dilated bronchi characteristic of bronchiectasis (fig. 2).

During the course of investigation of this patient he suffered 3 more hemorrhages losing 400, 300, and 500 cc. respectively. Treatment consisted of whole blood replacement, sedation, and the inhalation of oxygen.

A lower left pulmonary lobectomy was performed through a posterolateral thoracotomy incision, the seventh rib being resected. When the pleural cavity was entered it was noted that there was a heavy, soggy, triangular-shaped area of density in the midportion of the lower lobe. The base of this area was adherent to the parietal pleura over the dome of the diaphragm and the apex of the area extended to the hilus of the left lung. This corresponded to the anterior and posterior basal segments of the lobe. While the surgeon was freeing the adhesions at the base of the lobe, the anesthetist informed him that massive pulmonary bleeding was occurring, there being a rush of blood through the endotracheal tube. This was controlled by pressure on the pulmonary vessels at the hilus. The lobectomy was performed without further technical difficulty.

Figure 1. Roentgenogram showing slight elevation of left diaphragm with rounded area of density (traced on film) in lower lobe of the left lung overlying apical portion of cardiac shadow. Figure 2. Lateral bronchogram showing bronchiectasis of the lower lobe of the left lung.

The postoperative course was uneventful. The patient was returned to full military duty on 4 June after having completed a course of convalescent rehabilitation. Six months after operation he was found to be performing full military duty without difficulty.

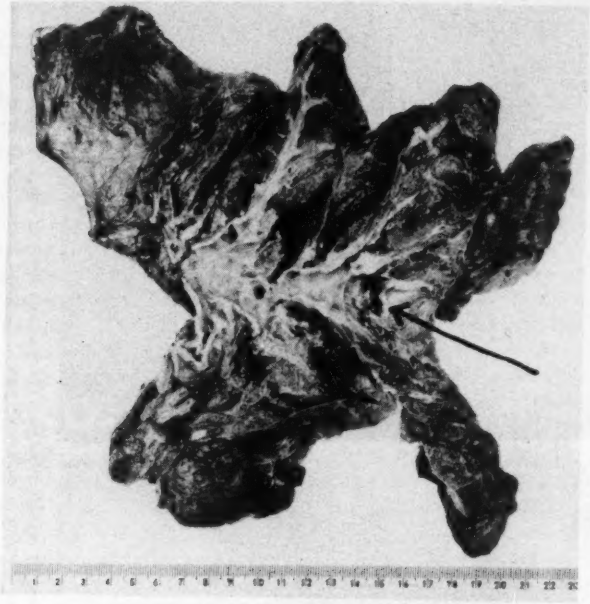

Figure 3. Resected lower lobe of the left lung revealing dilated bronchus.

Examination of the specimen revealed the triangular area of density already noted (fig. 3). Investigation in this area revealed dilated bronchi surrounded by parenchymal infiltration. The bronchus of the basal and medial portions of the lobe in its third division measured 2 cm. in diameter. At this point a blood clot from an eroded vessel, from which bleeding into the adjacent parenchyma and lumen of the bronchus had occurred, projected into the lumen of the bronchus (fig. 4). In addition to the vessel projecting into the lumen, multiple additional vascular channels were noted in the immediate vicinity. Microscopic examination revealed the source of bleeding to be an artery within the wall of the dilated bronchus, the arterial wall having been eroded so as to communicate with the lumen of the bronchus. The eroded vessel showed no signs of inflammatory disease. Evidence of chronic bronchiectasis and chronic pneumonitis was present in all sections from the involved areas.

Figure 4. Enlarged detail of figure 3 showing eroded vessel in dilated bronchus.

CONCLUSION

Although the chief symptom of bronchiectasis is usually cough with expectoration of large amounts of sputum over long periods of time, sudden massive pulmonary hemorrhage may be its presenting symptom.

BOOK REVIEWS

Tuberculosis of Bone and Joint, by *G. R. Girdlestone,* Sometime Nuffield Professor of Orthopaedic Surgery in the University of Oxford, and *E. W. Somerville,* M. B., F. R. C. S. (Ed.), Orthopaedic Surgeon to the Wingfield-Morris Orthopaedic Hospital, Oxford, From the Nuffield Orthopaedic Centre. 2d edition. 314 pages; illustrated. Oxford University Press, New York, N. Y., publisher, 1952.

Because no drug is available which will safely destroy all tubercle bacilli, the authors still firmly believe in the old and well-tried medical and surgical principles that have withstood the test of time. In this vein, they have combined the standard textbook approach with an unusual amount of personal warmth and enthusiasm. The book is divided into a broad discussion of general and local considerations of pathology, diagnosis, and treatment, followed by detailed analysis of individual joint lesions. The importance of adequate facilities such as the so-called "out-of-doors" hospital with a staff of trained personnel is stressed. Conservative versus operative treatment is discussed in great detail, the authors relating impressive facts and figures from their many years of experience. The controversial use of metallic internal fixation in arthrodesis is not mentioned. The management of cold abscess and Pott's paraplegia is well covered except for the role of antibiotics in the former. An appendix gives a well-illustrated description of splints and appliances which the authors have found useful. The book is abundantly illustrated, but many of the roentgenograms are of insufficient clarity.—*Maj. I. E. Rosen, U. S. A. F. (MC)*

Dynamic Psychiatry, Basic Principles, Volume One, by *Louis S. London,* M. D. 98 pages. Corinthian Publications, Inc., New York, N. Y., publisher, 1952. Price $2.

This book appears to be the first of an intended series by the author, under the general title, "Dynamic Psychiatry." It is not to be confused with another volume, edited by Alexander and Ross, recently published under the same title. This little volume consists of 5 chapters. Chapter I, entitled "The Evolution of Psychotherapeutics from Antiquity to the Time of Freud," is interestingly and informatively written. Chapter II, "The Meaning of the Dream," is a disappointment in view of the author's reputation in this field. The last 3 chapters are concerned with the psychology of the libido, the development of the libido in the child, and the libido in the adult. The author presents his concept of the libido theory and interprets psychiatric conditions in light of this concept. This book is clearly written and easily readable, but volume I alone is of little value for the general psychiatrist.

—*Commander S. V. Thompson, MC, U. S. N.*

Pregnancy With Sickle Cell Anemia and Placenta Accreta[1]

Robert D. Anspaugh, *Captain, MC, U. S. A.* (2)
Elmer C. Rost, *First Lieutenant, MC, U. S. A.*
Joseph W. Cleary, *First Lieutenant, MC, U. S. A.*

THE occurrence of sickle cell anemia in pregnancy is an unusual complication. Beacham and Beacham (3) reported a total of 53 cases in the literature prior to 1950.

CASE REPORT

A 23-year-old Negress (para I, gravida II) was first seen on 21 June 1951 in the prenatal clinic at this hospital. The last menstrual period started on 27 February. History revealed an uneventful antepartum course and the delivery of a 6¼ lb. boy 18 months prior to her first visit to this clinic. She gave no history of crises with her first pregnancy.

Routine blood studies were made and a diagnosis of sickle cell disease of which the patient had not been aware was established. The hemoglobin on 21 June was 7 grams per 100 cc.; the hematocrit was 27 percent, and the red blood cell count was 2,400,000. A serologic test for syphilis by cardiolipin microflocculation was positive. (The Johns Hopkins group reported that 7 of 11 patients "either had a positive serology or had been previously treated for syphilis" (4).) She was placed on a low sodium diet because one of the most frequent complications of this condition during pregnancy is toxemia. She was given special instructions as to the importance of an adequate diet. Vitamins and calcium were added to her diet. Because there is usually an iron-deficiency anemia associated with sickle cell disease, 0.3 gram

(1) U. S. Army Hospital, Fort Campbell, Ky.

(2) Assistant Professor of Obstetrics, University of Oklahoma.

(3) Beacham, W. D., and Beacham, D. W.: Sickle cell disease and pregnancy; review of the literature with analysis of experience at Charity Hospital, New Orleans. Obst. & Gynec. Surv. 6: 455-483, Aug. 1951.

(4) Anderson, G. W. (Baltimore), and Busby, T.: Sickle cell anemia and pregnancy. Am. J. Obst. & Gynec. 58: 75-89, July 1949. Cited in footnote reference (3).

of ferrous sulfate was given q. i. d. (The work of van der Sar *(5)* proved that the repeated administration of blood to these patients did not particularly alter the peripheral blood picture.) An attempt was made to keep the hemoglobin level at 8 grams or more per 100 cc. by means of transfusions. The dermatology section instituted treatment for the control of her syphilis, giving a total of 6,000,000 units of penicillin. Throughout her prenatal course she complained of abdominal cramping and pelvic joint pains of moderate to severe intensity. We were unable definitely to attribute these to her sickle cell disease. (This condition is characterized by many variable symptoms and is labeled by Winsor and Burch *(6)* as the "great masquerader.") The hemoglobin fluctuated widely throughout the prenatal course as a result of the 5 transfusions that were given. Her weight gain during the entire pregnancy was 21 lb.

She was admitted to the hospital in active labor on 9 December and was delivered by low forceps under low spinal anesthesia of a girl weighing 7 lb. 2 oz. Preparations for delivery consisted of having 500 cc. of crossmatched blood ready, giving an infusion of dextrose intravenously, and giving oxygen by mask. Having the intravenous needle in the vein proved to be a lifesaving procedure. The patient began bleeding profusely 15 minutes following delivery, losing an estimated 1,000 cc. of blood following which she went into shock with the blood pressure falling to 75/0. The crossmatched blood was given under pressure and additional blood was ordered. An attempt was made to remove the placenta manually, but this was unsuccessful because of the existence of a placenta accreta. The uterus was packed in the hope of decreasing the hemorrhage until sufficient blood could be administered to combat the shock. A total of 1,500 cc. of blood was given rapidly under pressure, the blood pressure rising to 118/62, but blood continued to ooze through the uterine pack. The patient was taken to surgery where a supravaginal hysterectomy was performed under general anesthesia. The added time that would have been required to perform a total hysterectomy was not considered justifiable. An additional 1,000 cc. of blood was given during and following the operation and the patient's condition improved. She returned to the ward in good condition. Sections of the uterus and placenta confirmed the diagnosis of placenta accreta. Her postpartum course was uneventful.

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(5) van der Sar, A.: Agemia con eritocitos en forma de hoz en la gestacion. Rev. Policlin. Caracas 12: 1-12, Jan.-Feb. 1943.

(6) Winsor, T., and Burch, G. E.: Sickle cell anemia, "great masquerader easily recognizable with routine use of diagnostic parameter. J. A. M. A. 129: 793-796, Nov. 17, 1945.

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